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THE BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

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BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

Vol. XLVIII. OCTOBER, 1954 No. 4.

SOCIAL ASPECTS OF DISEASES OF THE CHEST

BY A. LESLIE BANKS

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THE POSITION IN 1912

I HAVE recently been looking through the Interim and Final Reports of the Departmental Committee on Tuberculosis appointed in 1912 "to report at an early date upon the consideration of general policy in respect of the problem of tuberculosis in the United Kingdom."

The importance of the Committee is sufficiently shown by its constitution, for, under the chairmanship of Waldorf Astor, M.P., it included among its members Christopher Addison, N. D. Bardswell, Sir George Newman, Arthur Newsholme, James Niven, R. W. Philip, Jane Walker and Smith Whitaker. An Interim Report was rendered necessary by the fact that the National Insurance Act of 1911 came into operation on July 15, 1912, and the Final Report followed in March 1913.

After discussing the two aspects of the seed and the soil the Committee enumerated the factors which tended to weaken the defensive forces of the body, and proceeded to outline the five basic requirements to deal with the problem. They were agreed that any scheme should be available for the whole community; that those means which experience had proved to be most effective should be adopted for the prevention of the disease; that a definite organisation should exist for the detection of the disease at the earliest possible moment; that within practicable limits the best methods of treatment should be available for all those suffering from the disease, and that concurrently with these measures provision should be made for research.

It is interesting to note that Section 16 of the National Insurance Act provided the sum of 1s. 3d. per annum, in respect of each insured person, for the purposes of defraying the expenses of treatment, payable out of the insurance funds. A further sum of 1d. in respect of each insured person was available from the Exchequer, but was to be allocated by the Insurance Commissioners to research. It was estimated that this sum earmarked for research should amount to about £58,000 per annum, increasing in proportion to the natural increase in the number of persons insured. The duty was laid on the Insurance Committees to make provision for lectures and for the

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publication of information on questions relating to health, either directly or through existing local education authorities, universities or other institutions.

The comment was made in the Interim Report that " a large number of cases of pulmonary tuberculosis, and some cases of other forms of tuberculosis, can be treated in the patient's own home. For many of these cases the tuberculosis dispensary will be the centre for treatment." It was estimated that the capital outlay for adapting and equipping an existing house as a tuberculosis dispensary should not exceed £250 and often might cost considerably less. In order to attract the right type of men as chief tuberculosis officers " it will usually be found necessary to offer a salary of not less than £500 with prospects of increase." It was also thought probable that the cost of maintenance per bed in a sanatorium would be from 25 to 30 shillings a week, and that a certain number of Poor Law institutions might be taken over and beds in isolation hospitals adapted and utilised for the same purpose.

In the Final Report the Committee found it necessary to place on record their opinion that a properly conducted institution was not a source of danger to the neighbourhood. They also noted that the Chancellor of the Exchequer had announced that 6d. per insured person, out of the 1s. 3d. provided by Section 16 of the Insurance Act for sanatorium benefit, would be applied to the remuneration of general practitioners who would be concerned with the dispensary treatment and supervision of insured persons suffering from tuberculosis. While they welcomed this means of enlisting the hearty co-operation and interest of general medical practitioners, they regarded with some anxiety the smallness of the funds available.

With regard to prevention, the Committee were of the opinion that it was idle to hope that either infection would be entirely eliminated or that, apart from the discovery of some special process of immunisation, the resistant powers of human beings would be developed to such an extent that infection might be ignored. They recommended, as an effective means of preventing the spread of the disease, the compulsory isolation of certain cases which were in a state of high infectivity, and that steps should be taken to secure that all houses in which it was known that a person suffering from tuberculosis lived should be thoroughly disinfected at frequent and regular intervals. They also expressed the belief that " a healthy, sober, well-fed, well-clothed community is far less liable to infection from tuberculosis than one in which disease and drinking habits are prevalent, whose members are inadequately fed and clothed and in which houses are crowded and insanitary. It may broadly be said that an advance in material prosperity of the community as a whole will be reflected in a decreased incidence of tuberculosis."

Much attention was given to the prevention of bovine tuberculosis, including the possibility of pasteurisation of milk and the tuberculin testing of cattle, and the Committee found it necessary to recommend that farmers should be taught that tuberculosis in cattle is infectious and not hereditary.

They considered that research should be prosecuted over a wide field, and should include enquiries of a clinical, pathological, experimental, statistical and sociological character. Workers of proved and exceptional ability should be enabled to devote their whole time to research work, and should be given a definite and adequate salary and be entitled to a pension. Efforts should also

be made to retain for research work young and talented investigators who otherwise tended to drift into other lines.

The Position Today

Those Reports must be accepted as the most advanced opinion of the day. They were made at a time when tuberculosis caused some 10 per cent. of all deaths in England and Wales, as compared with 2·1 per cent. in 1952. In the latter year the deaths attributed to cancer of the lung outnumbered for the first time the deaths from respiratory tuberculosis, for there were three deaths assigned to the former cause for every two assigned to the latter. This increase is also well brought out in the following figures quoted by Ellman (1953) in a recent paper:

Lung Cancer and Respiratory Tuberculosis: A Comparison of Death-rates for England and Wales, 1947-1951

Year	*Respiratory tuberculosis*	*Cancer of bronchus and lung*
1947	19,753	9,535
1948	18,798	10,463
1949	17,388	11,272
1950	14,084	12,232
1951	12,036	13,233

With these figures in mind it may be of interest to examine some of the changes over the past forty years, and to try to relate these to the future requirements of the community.

The medical dictionaries of that time listed some thirty principal diseases of the lungs, of which the most important were pneumonia, which received the lion's share of attention, tuberculosis, syphilis and cancer. Under the last heading it was noted as early as 1894 (Quain's *Dictionary of Medicine*) that cancer of the lung was increasing in incidence. The changed position of pneumonia and syphilis, and the reasons for this, is too well known to require detailed consideration, but it should be noted that for women the mortality from respiratory tuberculosis in 1952 was less than one-third of the level as recently as 1938 and that for men it was just under half. The death rates of women aged 15-19 showed a relative improvement of 35 per cent. in the two years from 1950-52, and at ages 20-24 the improvement was 30 per cent.

Consider for a moment what has happened to the population as a whole. In 1912 the expectation of life at birth was 52 years for males and 55 years for females; forty years later it was 67 for males and 72 for females, an increase of 15 and 17 years respectively, thereby carrying large numbers of the population well into the so-called cancer age groups. At the same time the population of England and Wales has increased by eight millions. Over the same period there has been a considerable reduction in the number of people under 15 years of age with an increase of those between 15 and 65 years, and a dramatic increase in those over the age of 65.

In such a population, in which pneumonia, tuberculosis and syphilis no

longer dominate the disease pattern, other conditions hitherto almost hidden become revealed as the tide of mortality recedes, and the disability from " minor " conditions, such as chronic bronchitis for example, becomes of major importance.

It may not be inappropriate here to consider how the services envisaged in the Departmental Committee report have fared. It will be remembered that the first recommendation was that any scheme should be available for the whole community, but it is doubtful if any one of those authors, vivid and imaginative writers though some of them were, envisaged that less than forty years later there would be a comprehensive national health service in which the average patient-week cost in a non-teaching hospital would be £15 4s. 9d. per week, and in a teaching hospital would range from £18 13s. 9d. in the provinces to £24 18s. 8d. in London. Times have indeed changed since their estimate of 25 to 30 shillings a week, and the salary of £500 a year " with house," designed to attract the right type of medical superintendent, would now barely interest the right type of nurse.

Prevention and detection have blossomed in the unexpected directions of mass radiography and immunisation, and it would be interesting to know to what extent the modern range of treatment would fall within " practicable limits " as understood by the Committee. Its members would be scarcely less astonished to learn that the farmer, far from believing that tuberculosis is hereditary, is now becoming anxious lest his tubercle-free herds should become infected from human sources.

The Future

To attempt to be a prophet, even a minor one, in the field of medicine, is to invite ridicule, but it is not unreasonable to look round at the various landmarks and to speculate on the probable direction of the current trends.

If the present rate of decline of tuberculosis is maintained in this country it should become, like syphilis, a disease with a resistant hard core to be attacked as much by social and educational methods as by medical care. In those parts of the world where it is still out of hand the well-tried lines of attack laid down by the Committee of 1912 hold good.

If it is right, and it seems clear enough, that we are now entering, as a people, on our middle-age, what diseases may we expect and how are they to be dealt with ?

The most obvious is, of course, cancer of the lung. I cannot enter into a discussion of the causes because I am not fitted to do so, but I can at least point out what is perhaps obvious—that our present methods of dealing with the disease are both costly and ineffective. There were in 1952 about fourteen thousand deaths from cancer of the lung in England and Wales. The only known method by which those lives might have been saved would have been to remove the growth while it was still operable. It is doubtful whether any figures are available which would show precisely the cost to the community of the diagnosis, treatment and after-care of such patients, but it is not unreasonable to assume that it is at least of the order of £1,000 to £1,200 per case and possibly more. A small amount, perhaps in a

total annual budget of £450,000,000, but one which seems destined to grow rapidly.

Of the other diseases of the lungs which may affect an ageing population, apart from tuberculosis, probably the most important is bronchitis, and here we are again faced with a disease which on all counts, medical care, sickness benefit, absence from work and the like, is costly to the community.

It is interesting to speculate how the expert Committee of 1912 would have tackled these and allied problems. They would undoubtedly have agreed that medical care should be available for the whole community; they would also have plumped for early detection and the best methods of treatment; but, being realists and accustomed to think in terms of amounts of money much smaller than those with which we now deal, they would probably have decided that prevention, and research directed to this end, offered the most hope, both for the patient and for the community.

It is possible that they would have made a somewhat similar recommendation to that in the Final Report of 1913, when they advised that a Central Bureau should be established which should have a statistical and sociological department, in the work of which should be included the co-ordination and correlation of results.

Is it too fanciful to imagine that they would have recommended that the Regional Hospital Boards should be instructed to set up, in consultation with the universities in their areas, an Executive Committee which " should consist of not fewer than five nor more than ten members. The majority but not all of these members should be experts " to co-ordinate and correlate results and to undertake research of a clinical, pathological, experimental, statistical and sociological character ?

It seems to me that some such body, no matter what its title, organised on a regional basis, and producing annual reports in common form for purposes of comparison, might serve many useful purposes. On the statistical side it would bring out clearly regional differences in the mortality of the killing diseases and the morbidity of the disabling ones. The results of different methods of treatment could be compared together with their cost and, most important, a start might be made in tracing the social factors underlying the incidence of diseases of the lungs in an ageing population, with particular reference to prevention.

Such an " executive committee " would not, of course, draw its members only from the hospitals. The local health authorities would require to be represented, for their officers would have much information to contribute on domiciliary health and welfare. Equally important, the general practitioners, about whose " hearty co-operation " the 1912 Committee expressed concern, would find in such an organisation a local centre of information on these diseases.

What, in terms of practical politics, would be the desirable minimum of organisation ? First a central meeting place and a secretary. The former could be the offices of the Board and the latter one of its officers. Next, statistical advice and machinery; many Boards and Local Health Authorities now have this, and, in those areas which have not, arrangements could no doubt be made with the appropriate university department which would share in the

research. Cost would be limited to travelling and subsistence allowances for the members plus a relatively small annual outlay on stationery and reports.

It might be questioned whether such machinery is any more necessary for one group of diseases than another, and that rheumatism, for example, or cancer generally, would be more deserving of intensive study. Indeed, why not have a regional morbidity bureau to study all conditions ! The answer is that such an organisation as I have outlined, admittedly as an academic exercise, might lend itself well to a trial experiment. If it proved to be successful, and there seems to be no reason why it should not, the experience gained might be extended to other conditions than disease of the lungs.

Summary

In a nutshell, then, the suggestion has emerged, from a rather discursive discussion of some of the changes in diseases of the lungs since the reports of the Departmental Committee of 1912, that a simple organisation be set up, in the area of each Regional Hospital Board, to assess, statistically and sociologically as well as clinically, the incidence, causes and results of treatment of those diseases of the lung which may be expected to disable the community over the next forty years, with particular reference to their prevention.

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PULMONARY TUBERCULOSIS IN A RURAL SCHOOL AND COMMUNITY

A FOLLOW-UP STUDY

By G. M. Smith, Maude Maclellan and J. E. Hiltz

From the Department of Public Health, Nova Scotia, and the Nova Scotia Sanatorium, Kentville

Six years ago the routine follow-up of a case of tuberculous meningitis brought to light an outbreak of pulmonary tuberculosis in a rural school. The results of that investigation were reported elsewhere (Smith *et al.*, 1950) and are now briefly reviewed in order to recall the situation which then existed.

The investigation took place in the Fundy Division, one of eight Health Units into which the Province of Nova Scotia is divided. This Unit consists of the fruit-growing Annapolis Valley with a population of approximately 80,000, mainly rural. The people are of English and Scottish descent, with a few of Scandinavian origin. There are small Indian and Negro populations.

The Fundy Health Unit was organised in 1940 in order to supplement the work of the local authorities. It is supported entirely by the Province. Its staff, at the present time, consists of one medical officer, one supervisor of nurses, six field nurses, two sanitarians and three clerk-stenographers.

Unlike many other Provinces the tuberculosis case-finding programme is a responsibility of the Medical Officer in the Unit. Since 1940 chest clinics have been held twice yearly in various centres throughout the Unit. To these clinics come patients who have had pulmonary tuberculosis, their contacts and anyone else concerning whom the family physician desires an opinion in regard to the chest.

In addition to these travelling clinics, weekly chest clinics are held at the Unit headquarters in Windsor. The Nova Scotia Sanatorium is located at Kentville, the centre of the Unit, and twice weekly chest clinics are held there throughout the year. Thus there is available a constant service for case finding and follow-up.

For a considerable number of years the death rate for all forms of tuberculosis has been consistently lower in this Unit than in the remainder of the Province. At the time of the original paper, 1949, a rate of 20·2 per 100,000 population compared with 31·8 for the province as a whole. In 1953, however, the Unit rate of 13·8 is higher than the 10·9 reported for the Province. Nevertheless the rate is low.

Likewise, the results of tuberculin patch tests surveys show a relatively low incidence of infection, certainly in high school age groups tested. The percentage of positive reactors varied from 8·7 in 1943 to 19·6 in 1948 with a low of 5·4 being reached in 1952. The number of children so tested averages approximately 1,800 per year. It is felt that these percentages reflect the

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incidence of human type infection as the Province of Nova Scotia is a Restricted Area and there is little reason to believe there is much tuberculous infection among dairy herds.

In February 1948 this Department was consulted regarding a 9-year-old boy suspected of having tuberculous meningitis. The diagnosis was confirmed and the boy admitted to sanatorium, where he expired in May 1948. In the meantime his family contacts had been tuberculin tested by our Public Health nurse and all positive reactors X-rayed. One child, a sister, was found to have active pulmonary tuberculosis, primary type. This child eventually developed miliary tuberculosis followed by tuberculous meningitis resulting in death. Other family contacts were negative.

Not having found the source of infection, it was determined to investigate the school population by means of the Vollmer tuberculin patch test with the X-raying of positive reactors. This investigation revealed that of thirty-three pupils, nineteen or 57·6 per cent. reacted to the tuberculin test. Of the nineteen positive reactors seven showed a typical active primary complex, one had a pleural effusion and one a minimal active pulmonary tuberculosis. All the negative reactors and the school teacher yielded negative chest films.

Needless to say the homes of all the pupils showing disease were investigated, and after repeated visits by our nurse, several X-ray clinics held at the Nova Scotia Sanatorium and in the community, we discovered the following

TABLE I.—SUMMARY OF ALL CASES FOUND TO APRIL 30, 1949, ACCORDING TO AGE, SEX AND DIAGNOSIS

Age in Years	*Sex*	*Diagnosis*						
		Meningitis	*Miliary*	*Primary Active*	*Pleurisy with Effusion*	*Suspect*	*Pulmonary Tuberculosis Minimal*	*Pulmonary Tuberculosis Moderately Advanced*
3	F			1				
5	F	(1)	(1)	1				
6	F			1				
6	M			1				
6	F			1				
7	F			1				
8	M			1				
8	F			1				
9	M	1*						
9	F			1				
9	F				1			
10	F			1				
12	F			1				
13	M						1	
18	M							1
26	F							1
27	F				1			
33	M							1
Total	18	1	0	11	2	0	1	3

* Index case.

additional cases: Two moderately advanced cases of pulmonary tuberculosis, one of which was open, one female with a pleural effusion, one child (preschool) with a primary active type of infection. One additional child of school age had a conversion of her tuberculin patch test to positive with X-ray evidence of active primary infection. One other case of moderately advanced extent was discovered in an army recruit from a nearby village. It was learned that he had lived in the community the previous year and was a cousin of the original case of meningitis. He, in turn, infected his nephew, who was found to have an active primary infection. Thus the total cases of tuberculosis (all forms) found were as in Table I.

The present paper is concerned with the follow-up of the original cases and their family and school contacts for the period 1949 to 1954.

School

In our original report thirty-three children of school age comprised this group. Nine presented lung lesions, ten had positive patch tests without pulmonary disease and fourteen had negative tuberculin tests. Of this number twenty-six were re-examined in January 1954; six had left school and could not be found and one child of school age refused examination. All of the original group that could be located were followed at regular intervals by either the patch tuberculin test or X-ray from April 1949 to January 1954.

Of the original nine cases of pulmonary tuberculosis, seven made uneventful recoveries, five healing by calcification. One girl, age 15 years, has refused examination since 1951, her last diagnosis being primary tuberculosis, improved; one girl, age 7, made an uneventful recovery from her primary type infection, but was found to have a moderately advanced active tuberculosis in February 1952. Of the other ten positive patch tuberculin reactors, seven were examined with normal lung findings, two had left school and one is now in the army and presumed to be in good health.

Table II.—Original Negative Patch Tuberculin Test Reactors, 1950-54

Number Original Negatives	1950			1951			1952			1953			1954		
	Pos.	*Neg.*	*N.L.**	*Pos.*	*Neg.*	*N.L.*	*Pos.*	*Neg.*	*N.L.*	*Pos.*	*Neg.*	*N.L.*	*Pos.*	*Neg.*	*N.L.*
14	3	11	0	3	8	3	4	7	3	4	7	3	4	7	3

* N.L.: Not located.

Originally there were fourteen negative patch tuberculin test reactors. Table II indicates their tuberculin conversion by years. By 1954 seven still exhibited a negative reaction, three could not be located, and four had converted to positive—three of these within six months of the original survey and one four years later. All of these were exposed to cases within their homes and one developed a demonstrable active primary focus on X-ray. At the time of their last examination, January 1954, all showed satisfactory X-ray films.

During the period 1950-54 twenty-nine other children entered the school,

TABLE III.—TUBERCULIN PATCH TEST RESULTS OF NEWCOMERS TO SCHOOL, 1950-54

Year	Newcomers to School	Tuberculin Result	
		Positive	Negative
1950	13	3	10
1951	2	0	2
1952	1	0	1
1953	5	0	5
1954	8	4	4
Total	19	7	22

either by transfer from other sections or on reaching school age. Seven had positive tests when examined in school. However, six of these were contacts of known cases and had positive tuberculin patch tests before entering school; one new positive reactor was found. This was a boy who had moved into the district and who developed an active primary type of tuberculosis. His family contacts, with the exception of the father, were examined with negative findings. Two previous negative reactors converted to positive during the years, one being a contact of a known case.

Of the six known to be positive reactors on entering school, two had had primary tuberculosis. In January 1954 all X-rays were satisfactory, but two with previous negative films now showed hilar calcification.

CONTACTS

In 1949 direct contacts totalled forty-five. By January 1954 the total number of contacts had grown to fifty-eight, including those family contacts discussed above under the school section. Forty-two of these contacts were examined in January 1954. Of the sixteen not examined nine could not be located, five refused, one was in the army and one was dead of a non-tuberculous condition. Through the intervening years two previously negative adults had developed pulmonary tuberculosis. One of these is at the present in sanatorium undergoing treatment for far advanced tuberculosis, and the other has recovered from a minimal lesion after sanatorium treatment. One pleurisy with effusion case developed a minimal lesion, was treated in a sanatorium, discharged and a recheck in January 1954 showed reactivation of disease. All other contacts examined were well.

Originally there were sixteen indirect contacts examined—this number had grown to twenty-eight by 1954. The twelve new contacts were all examined with only seven of the original sixteen being done again. All those examined presented normal X-ray findings.

By 1949 three cases of moderately advanced pulmonary tuberculosis were found—two of these were proven active and open. In 1954 one of the latter had been in sanatorium under court order and at the present time is in a psychiatric hospital, his pulmonary condition being unchanged. The other was well. The third case was examined with a diagnosis of moderately advanced pulmonary tuberculosis, of questionable activity, being made.

Thus since April of 1949, in both the school and the contact group, five cases of pulmonary tuberculosis reinfection type have occurred. One was in a child with a previous primary type infection, two in previously negative persons, one was in a person who had previously had a pleurisy with effusion, and the fifth case found in April 1949 was thought to be the source of the outbreak. In addition two new active primary types of infection were discovered, although both show satisfactory films now. With the exception of one primary type infection all of these cases were related to each other and in turn to some of those children discovered in our original survey.

The total of all cases of tuberculosis found to date as a result of the follow-up of the original case of tuberculous meningitis is shown in Table IV.

TABLE IV.—TOTAL NEW CASES OF TUBERCULOSIS FOUND 1949 TO 1954, SUMMARISED ACCORDING TO DIAGNOSIS AND YEAR OF DISCOVERY

	1948	1949	1950	1951	1952	1953	1954	*All Years*
Primary { Active	8	4			1			13
Primary { Inactive				1	1		1	3
Pleurisy with effusion ..	2							2
Minimal Active	1	1			1†			3
Moderately Advanced Active	2*	1			1‡			4
Far advanced			1					1
Meningitis	1							1
Total	14	6	1	1	4	0	1	27

* 1 questionably active
† previous pleurisy with effusion } shown twice.
‡ previous primary active }

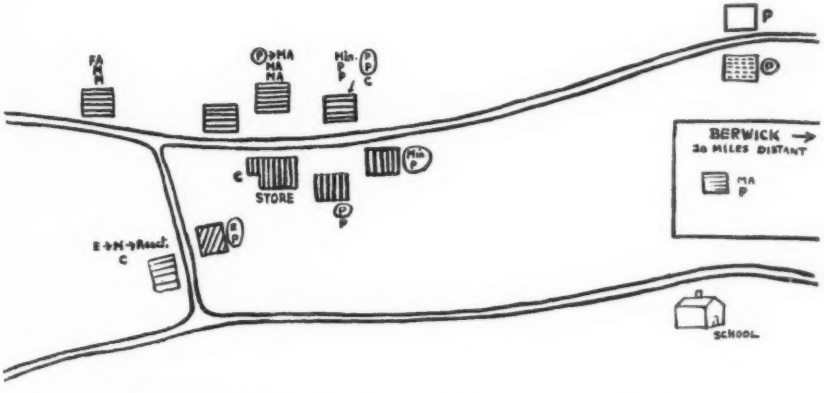

FIG. 1.—Sketch showing grouping of homes, school and store.

C—Calcification. Min.—Minimal. FA—Far advanced. P—Primary active.
M—Meningitis. MA—Moderately advanced. E—Pleurisy with effusion. S—Suspect.

Families closely related (parents and children) are shaded the same. Initials beside buildings indicate types of disease found therein. Initials in circles indicate original survey.

In order that the relationship of the majority of cases to each other and to the community be shown more clearly Figure 1 has been introduced. The original school survey group, nine in number, are circled—the investigation to date shows that eighteen of the total number of cases belonged to one family group, five others to a second family group. Both of these family groups lived quite near to each other and had in common the neighbourhood store. Two further cases came from one home in the immediate area. The remaining two cases were distinct from all of these, both in blood relationship and location of homes.

Summary

The results of the routine investigation of a case of tuberculous meningitis are reviewed. This paper is concerned with the five-year follow-up of the original cases and contacts, both adult and of school age.

By April 1949 seventeen other cases of tuberculosis had been discovered. The negative reactors contributed one case of active primary tuberculosis before April 30th of that year. Three of those that had conversion of tuberculin tests did so within six months of the original survey—all were contacts.

By January 1954 the total number of new cases discovered had risen to twenty-seven, including three children who then showed hilar calcification without previously having exhibited a pulmonary lesion. Later the original school group of cases contributed one reinfection type of moderately advanced pulmonary tuberculosis. Home contact investigation and follow-up yielded two previously unknown cases of post-primary infection pulmonary tuberculosis, one further active primary infection and one which went on from an effusion resolved to minimal active disease.

In five years twenty-nine other children came into the school. Although seven showed positive tuberculin patch tests when examined in school six of these were contacts with previous positive patch results. The seventh child developed a positive test while in school and X-ray examination revealed an active primary infection.

The need for detailed investigation and routine follow-up of every case and contact of pulmonary tuberculosis is demonstrated.

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TUBERCULOUS PLEURAL EFFUSIONS TREATED BY PROLONGED BED REST*

By Peter A. Emerson

From St. George's Hospital, London, S.W.1

The object of this paper is to show that in young adults the treatment of tuberculous pleural effusions by prolonged bed rest and sanatorium régime does not prevent some 30 per cent. of the cases progressing to further manifestations of tuberculosis.

Many follow-up series of pleural effusions have been published by various authors. Although they all agree that pulmonary and extrapulmonary tuberculosis occur frequently in the years following a pleural effusion, the actual figures reported vary considerably. The reported morbidity rates range between 66·3 per cent. (Borelius, 1933) and 7·5 per cent. (Kennedy and Melrose, 1949). The reported mortality rates vary between 24·3 per cent. (Farber, 1943) and nil (Kraft, 1949). These differences are due to the many variables in the selection, method and length of follow-up, and in the assessment of the material concerned.

The relevant publications have been studied and the different results are recorded in Tables 2, 3 and 4 in such a way as to standardise these variables as far as possible. By this means some comparison can be made between the various series.

It is now proposed to consider what these variables are and to what extent they have been standardised.

(*a*) *The Method of Follow-up.*—This may be by questionnaire alone (Arborelius, 1930; Trudeau, 1939), by clinical examination alone (Allard and Koster, 1911) or by clinical examination together with chest radiography (Borelius, 1933). Clearly the last method will reveal many pulmonary lesions which would remain undiscovered by questionnaire and clinical examination alone. The morbidity figures in Tables 2, 3 and 4 are, therefore, expressed in two columns. The first shows the total number of tuberculous lesions discovered by clinical examination together with chest radiography. The second gives the results obtained by clinical examination alone. The figures of Arborelius and of Trudeau, although obtained by questionnaire without clinical examination, are included in the second columns with a note to this effect. Both columns include extrapulmonary as well as pulmonary lesions.

(*b*) *The Completeness of the Follow-up.*—The number of the original cases untraced in any series has a bearing on the morbidity and mortality figures obtained. Most authors base their figures on the number traced. A large number of untraced cases can give misleading results. Only those series in

* This paper is based on part of a thesis accepted for the degree of M.D. (Cambridge).

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which more than 60 per cent. of the cases were traced are included in the tables. The percentage results are all estimated on the number of cases traced.

(*c*) *The Length of the Follow-up.*—This affects the morbidity and to an even greater extent the mortality figures obtained. It is well illustrated by the results of both Borelius and Kallner. Their follow-ups extended to seventeen and twenty years respectively, and the comparable times at which their patients developed or died of tuberculosis are shown in Table 1.

TABLE 1.—INCIDENCE OF PLEURISY IN THE PAST HISTORY OF CASES OF PULMONARY TUBERCULOSIS

Author and year	*Number of cases of P.T.B. studied*	*Percentage giving a history of pleurisy*	*Source of figures*
Allard and Koster (1911)	2,133	8·1	Routine records
Allard and Koster (1911)	2,123	30·6	Special inquiry
Kallner (1937)	605	19	Routine records
Press (1947)	3,134	9	Routine records

It will be seen that any morbidity figures may be expected to increase substantially with each year of follow-up to a total of about five years, after which far fewer cases will be revealed. Similarly the mortality figure will increase, but will continue to do so over a much longer period of time.

Series such as those of Kraft, where the follow-up was very short, have not been included in the tables (Kraft, 1949).

(*d*) *The Age Group of the Patients.*—Half of all cases of pleural effusion occur in the 15 to 30 age group (Scheel and Föien, 1928; Forsdat, 1951).

Most authors agree that the prognosis is better for those below 15 years of age than in the older age groups (Allard and Koster, 1911; Fauvet, 1945). There is further agreement that the prognosis becomes worse in those over 30 (Allard and Koster, 1911; Gsell, 1930; Fauvet, 1945; Forsdat, 1951).

As far as possible only cases in any series occurring in young adults between the ages of 15 and 30 have been included in Tables 2, 3 and 4.

(*e*) *Racial Origin of the Patients.*—Rich is of the opinion that there is little reasonable doubt that the negro race in general possesses a less effective resistance to tuberculous infection than does the white, or, in other words, a lower degree of racial resistance (Rich, 1951). It is to be expected, then, that the prognosis for the negro with a primary pleural effusion will be worse than for the white. Surprisingly enough, those American authors who have compared similar series in blacks and whites have found equally high, or even higher, morbidity rates for the whites, as compared with the blacks (Bonilla, 1942; Farber, 1943; Kraft, 1949). The mortality rates are, however, much worse in the blacks (Bonilla, 1942; Kraft, 1949). This higher mortality is probably in part explained by the higher incidence of extrapulmonary tuberculosis in the negro (Jones and Dooley, 1946). Those series dealing with negroes have been excluded from Tables 2, 3 and 4.

(*f*) *Radiographic Examination at the Time of the Effusion.*—There are two main

types of tuberculous pleural effusion. Firstly there are those that occur secondary to established post-primary tuberculosis, usually in the lung subpleurally, but sometimes in juxta-pleural lymph glands or even the spine. The lung foci will usually be seen on the chest radiograph.

Secondly there are those that occur as a late primary manifestation, usually within six months of the primary infection. In these cases the chest radiograph will usually show no parenchymal lung lesion. Occasionally, however, either the glandular or the parenchymal component of the primary complex, or even the complex itself, may be revealed. When only the parenchymal lesion is seen this group is indistinguishable from the type secondary to established post-primary bronchogenic tuberculosis, unless there is evidence of a recent Mantoux conversion or primary complex.

In 1928 Oeffner expressed the opinion that most of those cases of pleural effusion which developed progressive tuberculosis actually had a lung lesion at the time of the pleurisy (Oeffner, 1928).

Thompson also asserted that there was a difference in the prognosis between those cases with and those without an initial lung lesion (Thompson, 1947). He complained that most authors failed to differentiate the two types of case and separate their relative morbidity and mortality rates. To do this the initial examination of a pleural effusion must include chest radiography. To take this variable into account the follow-up series have been divided in the tables as follows:

Table 2 (*a* and *b*) shows those series of cases which were radiographed at the time of the pleurisy and found to have no visible parenchymal lung lesion. The table has been subdivided into two sections (*b*) and (*a*), depending on whether the patients were initially treated by prolonged bed rest or not. At present we are concerned only with the (*a*) section which lists those cases not treated by prolonged bed rest. Later the results listed in section (*a*) will be compared with those in section (*b*).

It will be seen that of all the cases with clear lung fields listed in Table 2 (*a*), 29·9 per cent. developed clinical or only radiographic evidence of tuberculosis, 12·1 per cent. developed only clinical tuberculosis, and 7 per cent. died. These figures demonstrate strikingly the very high incidence of subsequent tuberculosis in the years following pleurisy with effusion. The results in those cases with initial lung lesions are even worse.

Table 3 shows those series of cases which were radiographed at the time of the pleurisy and found to have a parenchymal lung lesion. It will be seen that of all the cases with initial lung lesions listed in Table 3, 35·9 per cent. developed clinical tuberculosis and 14·2 per cent. died.

It is apparent that those cases with lung lesions already present at the time of the pleurisy do show both a higher mean mortality rate (14·2 per cent. compared with 7 per cent.), and a higher mean rate of breakdown with clinical tuberculosis (35·9 per cent. compared with 12·1 per cent.), than do those cases without an initial lung lesion.

Table 4 shows those series of cases, whether radiographed or not at the time of the pleurisy, in which no division can be made between those with and those without an initial parenchymal lung lesion. These show a mean mortality rate of 15·2 per cent. and a mean rate of breakdown with clinical tuberculosis

TABLE 2.—FOLLOW-UP RESULTS OF YOUNG ADULTS WITH RADIOLOGICALLY CLEAR LUNG PARENCHYMA AT ONSET OF THE PLEURISY.

Author and year	*Number of cases traced*	*Percentage of cases traced*	*Years of observation*		*Total tuberculosis; clinical plus X-ray lesions only*		*Clinical tuberculosis only. Pulmonary and extra-pulmonary*		*Total deaths due to pulmonary and extra-pulmonary T.B.*	
			Minimum	*Maximum*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
(a) Cases NOT treated with prolonged bed rest:										
Oeffner (1928)	98	63	2	12	28	28	—	—	—	—
Arborelius (1930)	112	80	2	6	*Questionnaire*		21	18·7	10	8·9
Kallner (1937)	401	85	1	20	97	24·2	97	24·2	45	11·3
Bonilla (1942)	11	100	3	3	6	54·5	1	9·1	—	—
Farber (1943)	77	80	3	13	19	25	—	—	—	—
Robson (1944)	67	70	5	12	28	42	15	23	—	—
Fauvet (1945)	731	100	3	3	—	—	93	12·8	—	—
Brooks (1946)	117	100	1½	3	37	32	13	11	—	—
Jervall and Istre (1946)	152	99	1	5	—	—	17	11·2	9	5·9
Nilsen (1946)	109	97	1	10	12	11	—	—	4	3·7
Finkler (1947)	548	100	5	25	137	25	—	—	40	7·3
Press (1947)	1,192	100(?)	1	20	358	30	73	6·1	—	—
Maclean (1948)	107	94	3	5	—	—	17	15·9	—	—
Oille (1950)	78	100	5	8	34	43	—	—	4	5
Roper and Waring (1952)	141	100	5	6½	92	65	—	—	5	3·6
Mitchell (1953)	88	100	5	25	—	—	14	15·9	—	—
Totals and mean percentages:					848	29·9	361	12·1	117	7·0
(b) Cases treated with prolonged bed rest:										
Smith (1929)	89	99	4½	12	—	—	10	11·2	7	7·9
Jacquelin and Mallet (1935)	26	100	3	10	4	15·4	—	—	2	7·7
Trudeau (1939)	54	100	3	25	*Questionnaire*		6	11·1	2	3·7
Thompson (1946)	189	99	1	8	40	21·5	—	—	6	3·5
Maclean (1948)	49	71	5	7	15	30·6	—	—	—	—
Kennedy and Melrose (1949)*	41	85	5	14	—	—	3	7·5	2	5
Sibley (1950)	171	100	2	7	73	42·7	—	—	—	—
Totals and mean percentages:					132	30·3	19	10·6	19	4·1

* 25 per cent. under 15 years of age.

TABLE 3.—FOLLOW-UP RESULTS OF YOUNG ADULTS SHOWING A RADIOLOGICAL LUNG LESION AT THE ONSET OF THE PLEURISY.

Author and year	Number of cases traced	Percentage of cases traced	Years of observation		Total tuberculosis; clinical plus X-ray lesions only		Clinical tuberculosis only. Pulmonary and extra-pulmonary		Total deaths due to pulmonary and extra-pulmonary T.B.	
			Minimum	Maximum	Number	Percentage	Number	Percentage	Number	Percentage
Arborelius (1930)	13	87	2	6	Questionnaire		8	61·5	3	23
Trudeau (1939)	29	100	3	25	Questionnaire		9	31	1	3·4
Bonilla (1942)	9	100	3	3	—	—	6	66·6	4	44·5
Nilsen (1946)	29	100	1	10	—	—	13	44·8	4	14
Jervall and Istre (1946)	10	100	1	5	—	—	8	80	—	—
Thompson (1947)	40	100	1	5	—	—	12	30	5	11·5
Mitchell (1953)	76	100	5	25	—	—	18	23·7	—	—
Totals and mean percentages:					—	—	74	35·9	17	14·2

TABLE 4.—FOLLOW-UP RESULTS OF SERIES OF YOUNG ADULTS IN WHOM NO DIVISION CAN BE MADE BETWEEN THOSE WITH, AND THOSE WITHOUT, A RADIOLOGICAL LUNG LESION AT THE ONSET OF THE PLEURISY.

Author and year	Number of cases traced	Percentage of cases traced	Years of observation		Total tuberculosis; clinical plus X-ray lesions only		Clinical tuberculosis only. Pulmonary and extra-pulmonary		Total deaths due to pulmonary and extra-pulmonary T.B.	
			Minimum	Maximum	Number	Percentage	Number	Percentage	Number	Percentage
Hedges (1900)	130	61	2	8	—	—	56	43·6	29	22·3
Allard and Koster (1911) ..	514	90	2	28	—	—	245	47·7	115	22·5
Scheel and Föien (1928)	399	85	1	10	—	—	93	23·3	42	10·5
Gaarde (1930)	73	100	1	12	25	34·3	21	28·8	14	19·2
Gsell (1930)	79	87	1	6	—	—	30	38	12	15·2
Staissnie (1930)	93	100	¼	14	—	—	21	22·5	7	7·5
Borelius (1933)	184(156)*	84(68)	7	17	62†	39·8*†	41	26·3	28	14·5
Kallner (1937)	146	85	1	20	—	—	41	28·1	28	19·2
Sinding-Larsen and Heldaas (1947)	375	100	5	19	—	—	58	15	34	9
Landau (1949)	54	93	4	16	—	—	6	11	3	5·5
Totals and mean percentages:					87	38	612	30·3	312	15·2

* Borelius traced 184 cases but examined only 156. The morbidity percentages are therefore based on the 156 examined, and the mortality percentage on the 184 traced. † If minimal and doubtful lesions are included Borelius's morbidity figures in these columns become 100 per cent. and 66·3 per cent.

of 30·3 per cent. The figures are remarkably similar to those obtained in the cases known to have initial parenchymal lung lesions.

(*g*) *Treatment by Prolonged Bed Rest.*—The effect on the incidence of subsequent tuberculosis of treating the initial pleural effusion by prolonged bed rest is a controversial matter.

Before it was recognised that active tuberculosis frequently developed after a pleural effusion such cases were not kept at rest for longer than the immediate clinical condition of the patient required.

Although Grau provided no follow-up figures of his own, he recognised the frequent occurrence of subsequent active tuberculosis. To prevent this he recommended that patients with pleural effusions should be kept at rest for as long as possible, and then under surveillance for a year or more in order to detect any breakdown at an early stage (Grau, 1918). Similar advice has been proffered by other authors after they had found a high incidence of subsequent tuberculosis in their follow-up studies of such cases not given prolonged bed rest (Gaarde, 1930; Borelius, 1933). These authors, then, recommend prolonged bed rest because those patients not having it do badly. They provide no evidence that, had their cases had such rest, the results would have been any better.

The other and better approach to this problem is that of those authors who treated their cases with an adequate period of bed rest and then claimed improved follow-up results (Smith, 1929; Jacquelin and Mallet, 1935; Trudeau, 1939; Kennedy and Melrose, 1949). Their results are among those listed in Table 2 (*b*). The series of Smith is the only large one. His morbidity figure of 11·2 per cent. is not much less than the mean for all the series of cases not given prolonged bed rest and listed in Table 2 (*a*). His mortality figure of 7·9 per cent. is in fact higher than the 7 per cent. representing the mean of the mortality figures in Table 2 (*a*). The rather low figures of Kennedy and Melrose may be in part due to the fact that 25 per cent. of their cases were less than 15 years old. This younger age group is known to have a better prognosis. Falk, whilst giving no actual figures, claimed that in a three-year follow-up of his cases only 5 per cent. of them developed active tuberculosis. At the time of their effusions they had had six months' bed rest followed by a further three months' upgrading under sanatorium conditions (Falk, 1950). Other American authors recommend that bed rest should be continued for as long as six to twelve months (Roper and Waring, 1952).

Other authors have found no decrease in the incidence of subsequent tuberculosis in cases given adequate bed rest at the time of their effusions (Thompson, 1946; Maclean, 1948; Sibley, 1950). Their results are among those listed in Table 2 (*b*). Kallner's figures are not included in this table because 146 of his 547 cases were not radiographed at the time of their pleurisies and because no information was available about how many of the 73 patients who died had had sanatorium treatment (Kallner, 1937). Even so his results are most interesting. Of the 474 patients who were alive at the time of the follow-up study, 81 had had sanatorium treatment and 393 had not. Twenty-eight per cent. of the sanatorium treated cases had developed tuberculosis, whereas the figure was only 11 per cent. for those who had not had the benefit of such treatment. Kallner suggested that the apparently higher

tuberculosis morbidity rate in the sanatorium treated group might be the result of a reduced mortality rate. The mortality rate was unfortunately not known, but he produced some evidence to indicate that this was in fact lower in the sanatorium treated group. Thus in Kallner's series sanatorium treatment in no way reduced the number of patients subsequently sickening of tuberculosis, but possibly reduced the number who died.

In the light of these findings it is particularly interesting to note that the mean morbidity and mortality rates for all the cases in the series listed in Table 2 (*a*) (cases not given prolonged rest) are 29·9 per cent. and 7 per cent. respectively; the comparable figures obtained from Table 2 (*b*) (cases given prolonged bed rest) are 30 per cent. and 4·1 per cent. Apparently, prolonged bed rest makes no difference to the incidence of subsequent tuberculosis, but is possibly responsible for the reduced number of deaths in those cases given such prolonged bed rest.

With a view to obtaining further information on this subject 40 cases treated under ideal sanatorium conditions with prolonged bed rest have been followed up. The characteristics of the effusions under these conditions and the follow-up results will next be described.

The Present Investigation

(1) *Description of the Material*

The material consists of 40 cases of tuberculous pleurisy with effusion treated personally in an R.A.F. hospital. There were 36 males and 4 females, but in view of the predominantly male service population at risk this in no way represents a true sex incidence. All the patients were between the ages of 18 and 25 years except for one man aged 30 years.

In one case a second effusion occurred three months after the first. There are, therefore, 40 cases and 41 effusions available for study. Five of the effusions were very large, 31 were large and 5 moderate in size. Effusions less than moderate in size were not included in the series.

(2) *Criteria for Diagnosis*

Two patients were already in hospital at the time of onset of their effusions. One case (P.30) had had a severe primary infection three months previously and was still at bed rest. The other case (A.39) was upgrading after completing three months' bed rest for an area of tuberculous pulmonary infiltration. One case (A.32) was discovered by mass radiography.

In all the other cases there was an onset of pleurisy with effusion in an apparently healthy young adult. In no case was there any clinical evidence, such as a cough productive of purulent sputum, to suggest an underlying pneumonia or bronchiectasis as the cause of the effusion. In every case the Mantoux test was positive to first or second strength tuberculin, P.P.D.

The initial radiograph on admission to hospital showed a parenchymal lung lesion in 8 of the cases; in at least one this represented the remains of a recent primary complex. In the other 32 cases the lung fields were clear.

In every case the presence of a pleural effusion was confirmed by the diag-

nostic aspiration of clear straw-coloured fluid. In all cases the dominant cell was the lymphocyte.

Tubercle bacilli were demonstrated in the pleural fluid by guinea-pig inoculation or culture examination in only 6 cases; and in the sputum or gastric washing in a further 7 cases.

Definite tuberculous infiltration was present in the lung, without a positive sputum or pleural fluid, in a further 4 cases; in one other the peel after decortication showed definite histological evidence of tuberculosis. Thus in 18 (45 per cent.) of the 40 cases there was definite evidence confirming the tuberculous ætiology.

(3) *Description of Treatment*

All the cases were treated at strict rest for at least three months after which, if there were no contra-indications, slowly increasing activity was allowed over a further three months.

In every case a small quantity of fluid was removed for initial diagnostic purposes. Therapeutic aspiration was carried out early in 7 cases on account of pressure symptoms, mediastinal displacement or extension of the fluid over the apex of the lung, and in 5 cases when there had been no clearing of the fluid after five weeks' bed rest.

In one case an operation for decortication of the lung was performed 180 days after the onset of the effusion. Gross pleural thickening was encountered and removed piecemeal. Histological examination showed a dense mass of collagenous fibrous tissue containing considerable numbers of giant cells and small lymphocyte aggregations. The post-operative course was not smooth. He developed a bronchial fistula and an empyema which had to be drained. The external sinus did not close finally until two years after the operation, and over three years after the onset of the effusion there was still gross pleural thickening.

(4) *Assessment of Progress and Response to Treatment*

The response to treatment was assessed by the following observations:

(i) The duration of the pyrexia.

(ii) The duration of an accelerated E.S.R.

These observations are not of present interest. They will be reported elsewhere as controls against which to compare the results of streptomycin and P.A.S. therapy in a series of tuberculous pleural effusions (Emerson, 1954).

(iii) The duration of the pleural fluid.

Every case was radiographed on admission to hospital and subsequently at least every four weeks during his stay in hospital. After discharge radiographs were taken at the discretion of the various chest physicians following up the cases, usually every three months for the first year and thereafter at longer intervals. The serial radiographs were studied and an assessment was made of the times from the start of bed rest to the first radiographs showing complete clearing of the effusions to have taken place and left no more than obliteration of the costo-phrenic angles. It was possible to trace this eventual clearing in

all the cases except the one in which a decortication was done after 180 days (P. 9). Clearing had still not occurred more than three years (1,160 days) after the onset of the effusion.

(5) *Incidence of Subsequent Tuberculosis*

After discharge from hospital all the cases were referred to the out-patient care of their local chest clinics. From time to time letters were written to the various chest physicians requesting information about the patient's progress and the loan of the chest radiographs. When the patients moved from one area to another the new chest physician was contacted. All the patients remained under surveillance.

The duration of the follow-ups is estimated as the time from the onset of the effusions to the most recent chest radiographs and examinations by the chest physicians. These times in months are recorded in Table 6 together with the progress and fate of the patients.

All 40 of the cases have been followed up for at least two years, 25 for at least three years, 7 for four years and 2 for five years.

Of the 40 cases, 12 (30 per cent.) have developed further manifestations of tuberculosis. These have occurred as follows:

1 case developed tuberculous cervical adenitis.
2 cases developed later contralateral effusions.
1 case developed a later homolateral effusion followed by tuberculous pulmonary infiltration.
8 cases developed tuberculous pulmonary infiltration.

The times at which these various manifestations presented are recorded in Table 6. At the most recent follow-up examinations all these tuberculous

TABLE 5.—INCIDENCE OF FURTHER MANIFESTATIONS OF TUBERCULOSIS DURING THE FIRST 1, 2, AND 3 YEARS AFTER PLEURISY WITH EFFUSION

Time after the onset of the effusion	*Number of cases followed for at least these times*	*Cases developing further manifestations of tuberculosis*				
		Pulmonary tuberculosis	*Pleural effusion*	*Extra-pulmonary tuberculosis*	*Total*	
					Number	*Percentage*
(a) Cases with initially clear fields:						
First 1 year	32	4	3	0	7	21·9
First 2 years	32	5	3	1	9	28·1
First 3 years	19	6	1	1	8	42·1
(b) Cases with initial lung lesions:						
First 1 year	8	0	0	0	0	0
First 2 years	8	0	0	0	0	0
First 3 years	6	1	0	0	1	16·7
(c) Total cases with and without initial lung lesions:						
First 1 year	40	4	3	0	7	17·5
First 2 years	40	5	3	1	9	22·5
First 3 years	25	7	1	1	9	36

TABLE 6

Case No.	*Lung fields on X-ray*	*Time in days for X-ray clearing*	*Progress of the patients and time, in months after the onset of the effusions, of:* (1) *The occurrence of further manifestations of tuberculosis*	(2) *the most recent follow-up*
P. 1	Clear	100	Developed active minimal P.T.B. at 25 m. Well at	35 m.
P. 2	Clear	110	Developed active minimal P.T.B. at 38 m. Well at	46 m.
P. 3	Clear	300	Remaining well at	27 m.
P. 4	Clear	180		37 m.
P. 5	Clear	180		28 m.
P. 6	Clear	900		30 m.
P. 7	Clear	660	Developed active P.T.B. at 12 m. Well at	60 m.
P. 8	Clear	120	Remaining well at	30 m.
P. 9	Clear	1,160+		38 m.
P. 10	Clear	90		24 m.
P. 11	Clear	340	Developed active P.T.B. at 10 m. Well at	40 m.
P. 12	Clear	330	Remaining well at	49 m.
P. 13	Clear	690		31 m.
P. 14	Clear	540	Developed active P.T.B. at 29 m. Well at	47 m.
P. 15	Clear	60	Developed active P.T.B. at 2 m. Well at	26 m.
P. 16	Clear	180	Remaining well at	28 m.
P. 17	Clear	30		38 m.
P. 18	Clear	80		46 m.
P. 19	Clear	630	Developed a contralateral effusion at 6 m. Well at	30 m.
P. 20	Clear	480	Developed T.B. cervical adenitis at 15 m. Well at	36 m.
P. 21	Clear	320	Remaining well at	38 m.
P. 22	Clear	80		51 m.
P. 23	Clear	50		30 m.
P. 24	Clear	70	Developed active P.T.B. at 3 m. Well at	50 m.
P. 25	Clear	30	Remaining well at	30 m.
P. 26	Clear	120	Developed active P.T.B. at 14 m. Well at	42 m.
P. 27	Lung lesion	140	Remaining well at	42 m.
P. 28	Lung lesion	330		46 m.
P. 29	Lung lesion	50	Developed active P.T.B. at 32 m. Well at	65 m.
P. 30	Lung lesion	230	Remaining well at	47 m.
A. 31	Clear	30	Developed a homolateral effusion at 3 m. and active minimal P.T.B. at 28 m. Well at	38 m.
A. 32	Clear	1,200	Remaining well at	40 m.
A. 33	Clear	210		37 m.
A. 34	Clear	190		24 m.
A. 35	Clear	470		41 m.
A. 36	Clear	80	Developed a contralateral effusion at 12 m. Well at	42 m.
A. 37	Clear	20	Remaining well at	27 m.
A. 38	Lung lesion	60		27 m.
A. 39	Lung lesion	130		48 m.
A. 40	Lung lesion	50		30 m.
A. 41	Lung lesion	120		53 m.

lesions had been successfully treated and in all the cases the disease was regarded as quiescent and the patients were well and fit for work.

If those cases with and without initial lung lesions are considered separately it will be seen that of the 32 with initially clear lung fields 11 (34·4 per cent.) developed further manifestations of tuberculosis, whereas of the 8 with initial lung lesions only 1 (12·5 per cent) broke down.

All these figures relate to the total number of further manifestations of tuberculosis and do not take into account the different lengths of the follow-up in the various cases.

Table 5 shows the incidence of further manifestations of tuberculosis in the first year, in the first two years and in the first three years after the onset of the effusions in the cases followed up for at least these times. It will be seen that only 25 cases were followed up for as long as three years. Thus the figures for the first three years refer only to these 25 cases.

As has already been stated, one case developed a homolateral effusion at three months, followed by tuberculous pulmonary infiltration at twenty-eight months. This effusion is included in the first-year figures, and only the tuberculous pulmonary infiltration in the third-year figures. To have included in the third-year figures both the effusion and the subsequent infiltration would have made the result misleadingly high.

It will be seen that further manifestations of tuberculosis had appeared in 7 (17·5 per cent.) of the 40 cases by the end of the first year and in 9 (22·5 per cent.) of the 40 cases by the end of the second year. Considering only those cases with initially clear lung fields, further manifestations of tuberculosis had appeared in 7 (21·9 per cent.) of the 32 cases by the end of the first year and in 9 (28·1 per cent.) of the 32 cases by the end of the second year.

Conclusions

The presenting features of the cases described are in no way remarkable and this aspect of the study will be considered no further.

The various times taken for clearing of the fluid to take place are of interest. It will be seen from Table 6 that in 4 cases such clearing had occurred by the thirtieth day, in 8 cases it took over 1 year, in 4 cases over 2 years and in 2 cases over 3 years. One (A.32) of these last two cases was originally discovered by mass radiography and clearing finally occurred by the 1,200th day after diagnosis. The other was the patient who had an operation for decortication of the lung with a subsequent bronchopleural fistula and empyema and had still not cleared by the 1,160th day. This then was the only case in which clearing did not occur during the observation period. All the rest did clear although some took several years to do so.

No similar observations on the eventual clearing of pleural fluid or thickening, when observed for a sufficiently long time, have been encountered in the literature. The findings do, however, conform to clinical impressions. Anstie, as long ago as 1871, stated that retraction of the chest wall was usual with large effusions but that this commonly righted itself, especially in children, within one or two years (Anstie, 1871).

It may be noted at this point that one of the arguments put forward by those who advocate the routine early aspiration of pleural effusions is that such treatment prevents gross pleural thickening and chronic unresolved effusions. If, as the present study suggests, practically all effusions clear spontaneously provided that they are given sufficient time, then this particular argument for early aspiration loses all its force.

Although all the patients in this series were treated with adequate bed rest the follow-up results are disappointing.

Reference to Table 2 reminds us that, of all the cases from the literature with initially clear lung fields, the number subsequently developing further manifestations of tuberculosis is 30·3 per cent. for those treated with adequate bed rest, and 29·9 per cent. for those not having such treatment.

The present study gives very similar results whether we use the figure of 34·4 per cent. for those with initially clear lung fields or that of 30 per cent. for the group as a whole. Thus bed rest for the times employed in these cases had no apparent effect on the incidence of the subsequent manifestations of tuberculosis, which might have been expected had the cases not been treated with adequate initial bed rest.

These findings are especially disheartening when it is remembered that these patients were treated under ideal conditions. They were on full pay and allowances, and there was no pressure to get them up too soon because of financial difficulties or bed shortages, as is sometimes the case in civilian practice.

On the other hand, it is interesting to note that at the most recent follow-up all those who had developed and been treated for further manifestations of tuberculosis were found to be well and their disease quiescent. It may be that the initial bed rest was a factor in this satisfactory outcome, but it seems more likely that it is due to the regular follow-up carried out by the chest clinics. The fresh lesions were all recognised in their early stages and energetically treated. Even so, one patient required a pneumonectomy and another a thoracoplasty. All the others responded to rest and antibacterial therapy alone.

Whatever the explanation may be, the initial treatment of these effusions was unsatisfactory because it did not prevent a third of them developing further manifestations of tuberculosis in the ensuing two to five years. Some other treatment is clearly necessary to prevent this occurring in such cases.

It is suggested that treatment of the initial pleurisy with streptomycin and P.A.S. or I.N.A.H. might prevent this high incidence of subsequent tuberculosis.

Summary

The high incidence of active tuberculosis in the years following pleurisy with effusion is considered.

Selected data from all the main published follow-up series are tabulated in such a way as to standardise the variables which are responsible for the different results obtained by the various authors.

It is concluded that in the years following pleurisy with effusion in young white adults 29·9 per cent. develop clinical or only radiological evidence of tuberculosis, 12·1 per cent. develop only clinical tuberculosis and 7 per cent. die. The results are worse in those cases with lung lesions at the time of the initial pleurisy; 35·9 per cent. develop clinical tuberculosis and 14·2 per cent. die.

A comparison is made between the results in those series of cases given prolonged bed rest at the time of the initial pleurisy and those not having the benefit of such treatment. Prolonged bed rest at the time of the pleurisy did not reduce the incidence of subsequent tuberculosis in these series of cases.

Forty personally treated cases of tuberculous pleurisy with effusion in young

adults have been studied and followed up for two to five years. The times taken for the fluids to clear and the incidence of subsequent tuberculosis are recorded.

It is concluded that practically all tuberculous effusions clear spontaneously provided that they are given sufficient time to do so. It may take several years.

In spite of prolonged rest under ideal conditions at the time of the initial pleurisy, 12 (30 per cent.) of the cases developed further manifestations of tuberculosis.

It is concluded that some treatment other than prolonged bed rest is necessary to prevent this high incidence of subsequent tuberculosis.

It is suggested that antibacterial therapy with streptomycin and P.A.S. or I.N.A.H. may provide an answer to this problem.

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TUBERCULOSIS AND COALWORKERS' PNEUMOCONIOSIS

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1. Introduction

This subject, difficult enough in itself, is bedevilled by our continued ignorance about some aspects of coalworkers' pneumoconiosis. There is general agreement, at least in Western Europe, that the changes seen in the X-rays of coalminers can be classified into two groups—" simple pneumoconiosis " and " progressive massive fibrosis " (P.M.F.). In " simple pneumoconiosis " there are generalised minute opacities whose profusion is related to dust exposure (Roach, 1953) and which do not increase after dust exposure has ceased. In " progressive massive fibrosis " (P.M.F.) there are localised, larger opacities which tend to grow and fuse to form large, massive shadows whether or not dust exposure is continued (Davies *et al.*, 1949). The pathologists make a similar distinction between generalised focal dust deposits and large areas of dense collagenous fibrosis, but there is some difference of opinion between the British and Continental schools in detail. The latter believe that the nodules of simple pneumoconiosis, seen in the lungs of coalworkers, although different from the silicotic nodule, are really silicotic nodules modified by the presence of coal dust. They therefore prefer the name " silicosis " or " anthracosilicosis " to " coalworkers' pneumoconiosis." No clear-cut views have been expressed by this school on the etiology of P.M.F., but tuberculosis is generally believed to play some, although possibly not the chief, role. British authorities (Gough, 1947; Heppleston, 1951) describe simple pneumoconiosis of coalworkers as a mild fibrotic reaction to coal dust retained in the lung forming a " coal macule," which is different from the more fibrotic silicotic nodule. They consider P.M.F. to be a form of tuberculosis modified by the presence of coal dust. The hypothesis is, in brief, based upon the similarity between tuberculosis and P.M.F. radiologically and pathologically, the finding of a high percentage (up to 40 per cent.) of positive T.B. cultures in consecutive series of post-mortems on miners with P.M.F., and the fact that the appearance and progression of P.M.F. appears radiologically to be independent of dust exposure.

One of the difficulties in the tuberculosis hypothesis is that in life (Cochrane *et al.*, 1952) only 1 per cent. of cases of P.M.F. have a positive sputum and in them the prognosis is grave (Kilpatrick *et al.*, 1954). This partly accounts for the higher proportion of post-mortem cases with positive bacteriological findings, and it has been suggested that P.M.F. with a positive sputum is a secondary tuberculous infection of a previously non-tuberculous process. However, in

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the non-mining males the vast majority of tuberculous lesions appear radiologically before the age of 30 (Springett, 1951), while the peak of the male death rate is about 50. It therefore seems probable that many lesions remain apparently quiescent for many years before becoming overtly infectious and progressive.

Throughout this paper the " tuberculosis " hypothesis has been accepted as the simplest explanation of the facts as we know them at present.

This hypothesis is at present being investigated by epidemiological means in the Rhondda Fach Scheme (Cochrane *et al.*, 1952). Some preliminary findings derived from this scheme and other epidemiological sources form the basis of this paper.

2. Historical

The historical development of the idea that coal dust inhalation in some ways modifies the response of the lung to tuberculous infection is of some interest.

One of the earliest as well as one of the most interesting references is the observation of Clapier (1763). He told the story of an artisan of the village of Alais who, having been diagnosed as suffering from phthisis on the basis of cough, fever and purulent sputum, received routine hospital treatment; however he lost weight so rapidly that he was finally advised to go and live underground in a coal mine. The results were striking. His sputum decreased and became covered with a fine black powder, and he finally became afebrile, put on weight, and after a period of light work underground, returned to the surface cured. Clapier also referred to Willis as affirming that phthisis was less rampant in countries where charcoal was burnt, and to an English doctor who had observed that there was no tuberculosis amongst English coalminers. Unfortunately, he gave no detailed reference.

Clapier himself interpreted this surprising cure as due to the effect of sulphur, which was a fashionable drug at the time, and which he believed to be an important constituent of the air in coal mines.

Beddoes and Watt (1796) were thinking along the same lines when they suggested that " Darwin's dusting box " might be used to " coat the pulmonary ulcers with fine charcoal." It is not, however, recorded whether the idea was ever put into operation.

In the nineteenth century there are a very large number of references in the French, Belgian and German literatures to the belief that phthisis was rare or non-existent among coalminers. Valat (1835) declared that he had never seen a case of phthisis among miners. He looked after 500 miners for eight years in the Pas-de-Calais coalfield. Demarquette (1861) came to the same conclusion in the same area. In Belgium, François (1861) thought phthisis was non-existent among miners, Riembault (1862) in his monograph thought it was a great rarity, and Crocq (1862) returned to the idea of treating tuberculosis with inhalations of coal dust.

In Germany, excellent figures are available from the " Knappschaften " records. Seltmann (1866) thought tuberculosis a rarity amongst miners, as did Brockmann (1845), Schirmer (1859), Merkel (1882) and Schlockow (1881).

In Great Britain, Greenhow (1864) noted that pulmonary infections amongst miners tended to be less toxic and less progressive than amongst other workers. Cox (1857), however, states that " tuberculous consumption and its too well known career is very frequently met with amongst colliers." We can, however, conclude that the general medical opinion in the eighteenth and nineteenth centuries was that coalminers had a low mortality rate from tuberculosis.

In this century there has been considerable discussion about the tuberculosis mortality rates of coalminers. At the beginning the majority thought coal dust had a beneficial effect, but as it became apparent that coalminers, particularly in South Wales, were suffering from a disabling pulmonary disease, the opposite view gained ground. The extensive literature has been very adequately reviewed by Hart and Aslett (1942).

3. Epidemiological Studies

(i) *Terminology*

The present confusion in epidemiological terminology necessitates a few explanations. The word " incidence " has been, and still is, used in so many different senses that its meaning has become blunted. It has therefore been avoided. " Attack rate " has been used rather than " inception rate," as recommended by Stocks (1949) for chronic diseases, as it does not seem really necessary to have two phrases for the same rate, and " attack rate " is a pleasanter phrase. " Prevalence rate " has been used rather than " morbidity rate " to describe the number of persons per 100 (or per 1,000) of a defined group who have a particular characteristic at a particular time. " Morbidity " implies the existence of a " disease " and is better avoided when one is dealing with radiological abnormalities. Case fatality and mortality are used in the usual senses.

(ii) *Mortality Rates for Tuberculosis*

The evidence so far suggests that in early days of mining the tuberculosis mortality of miners was low compared with that of other males, but that the miners have more recently lost—or are losing—this favourable position. This suggests that some occupational factor (selection or environment) was affecting either the case fatality or attack rate of tuberculosis or both of miners in the early days.

The tuberculosis mortality rates for coalminers were on the whole low in 1921 (Standardised Tuberculosis Mortality Rate (SMR.)=70: Registrar-General's Reports 1926), but there were marked regional differences.

The 1931 Census confirmed the previous findings (SMR.=79), and when the mortality of miners' wives was used as a control, showed that the low tuberculosis mortality rates of coalminers (apart from anthracite miners in the western part of Wales) were due to occupational environment or selection and not to the general environment which would affect men and women equally (Registrar-General, 1938). American figures (Lanza and Vane, 1939) give the same general picture—*i.e.*, low tuberculosis mortality rates for all miners except those working in anthracite.

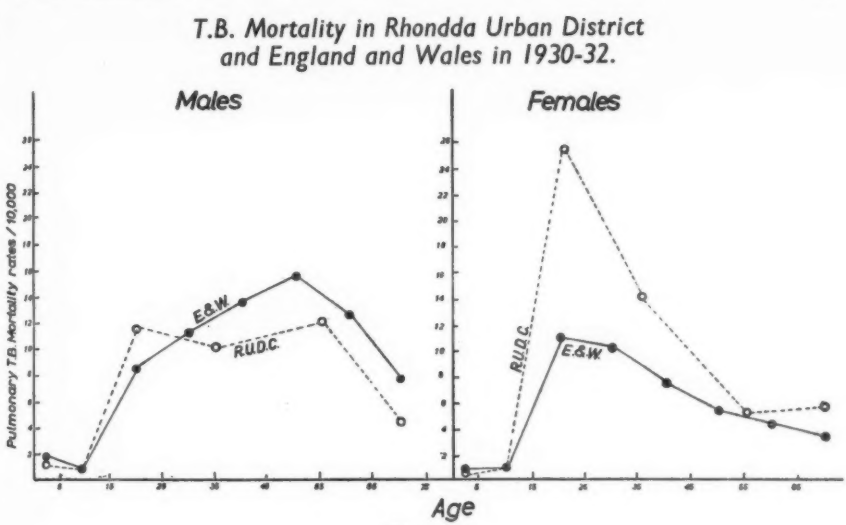

FIG. 1.

It has been argued that these low tuberculosis rates for miners were due to occupational selection of the fitter men for mining, but if this were so the low tuberculosis rates for males would disappear if the mortality experience of a whole mining community instead of that of miners only were considered. Fig. 1 shows the tuberculosis death rates for males and females for the Rhondda Urban District for 1930-32, compared with the figure for England and Wales as a whole for the same period. The female death rates for the Rhondda, as one would expect from the social and economic conditions prevailing there at the time, were much higher than those for England and Wales, while there was very little difference in the males. This clearly does not support the hypothesis of the fittest (as regards tuberculosis) going into mining while their weaker brethren do the other jobs.

More direct evidence against occupational selection can be extracted from the Registrar-General's 1931 data. Fig. 2A shows a comparison between Tuberculosis death rates of " hewers and getters " and " other underground workers " (Registrar-General, 1938). It is seen that the colliers have much higher rates than the other group, and as the colliers are the most " occupationally selected " as well as being better off economically, there is little support for the " occupational selection " theory. Fig. 2B shows a comparison between the tuberculosis death rates of the " other underground workers " and the various economic groups in England and Wales. It demonstrates how very favourable their tuberculosis rates are, as miners are classified in Social Class III.

More recent figures from the Rhondda Urban District (Fig. 3) suggest that this favourable trend amongst Rhondda males is disappearing. Fletcher (1948) has argued that pneumoconiosis has recently been increasing in the area, so the evidence suggests that an increased prevalence of pneumoconiosis may be associated with the disappearance of the favourable trend.

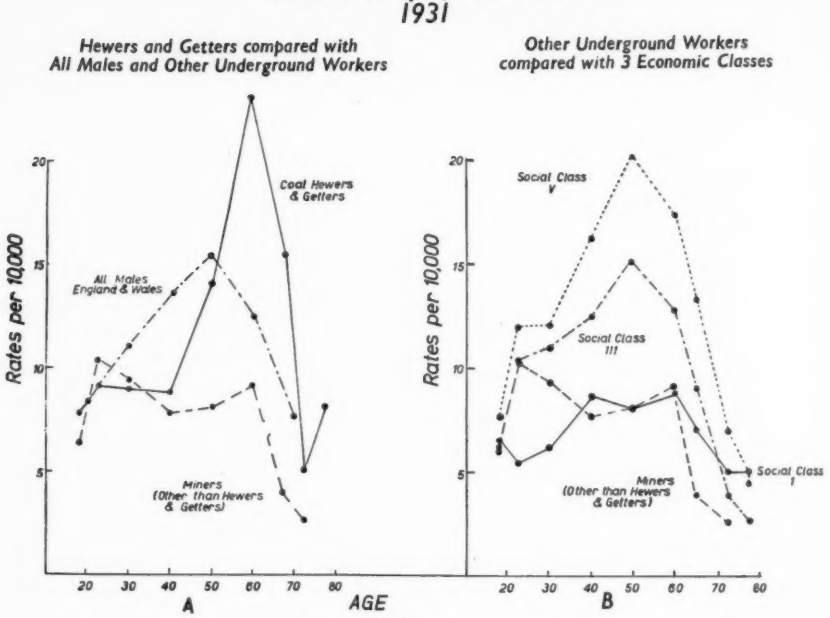

FIG. 2.

This evidence confirms the idea that the favourable mortality of miners is disappearing, and it also suggests that the most favourable mortality is enjoyed more by " other workers underground," who have a smaller dust exposure, than by the colliers. A possible explanation of all this is that a slight exposure to dust decreases the attack rate, or the case fatality—or both—while a further increase in dust exposure either increases the attack rate or increases the case fatality—or both.

(iii) *Attack Rates of Tuberculosis and P.M.F.*

Evidence has been accumulating that the attack rate is influenced by the category of pneumoconiosis in the original X-ray. Fletcher (1948) in his Goulstonian Lecture made the suggestion that P.M.F. only appeared on an X-ray showing category 3 simple pneumoconiosis. This was confirmed by Davies *et al.* (1949), and calculations based on their figures suggest an attack rate of about 2·5 per cent. per year. Mann (1951), using somewhat selected material, found an annual attack rate (of tuberculosis and P.M.F. combined) of 0·5 per cent. for miners without pneumoconiosis (category 0), 2·5 per cent. for miners with simple pneumoconiosis of categories 1 and 2, and 6 per cent. for those with category 3. Cochrane *et al.* (1951), following-up a well-defined pit population, found a combined (tuberculosis and P.M.F.) attack rate of 2·5 per cent. for categories 2 and 3, but the population was too small to measure an appreciable attack rate in categories 0 and 1. The evidence about the attack

Male T.B. Mortality in Rhondda Urban District and England and Wales

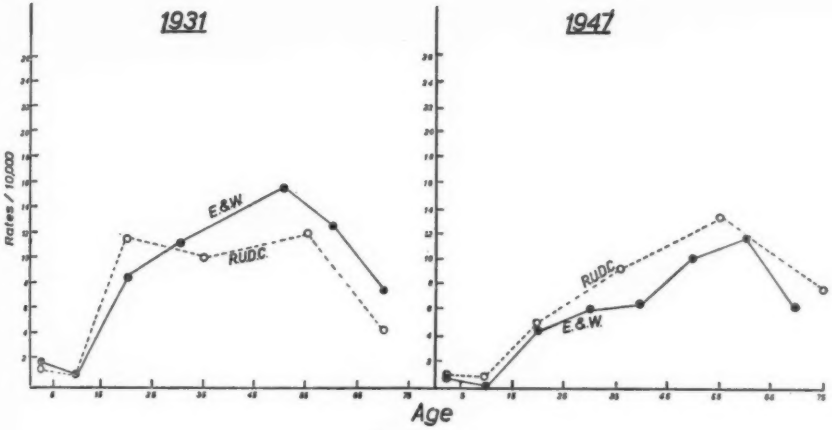

FIG. 3.

rate of pulmonary tuberculosis in males has been summarised by Springett (1951). The general opinion is that the annual rate is in the neighbourhood of 0·2 per cent. per year, so this combined attack rate of P.M.F. and tuberculosis appears to be at least tenfold greater. It must, however, be remembered when comparing " attack " rates that they are very sensitive to differences in age distribution in the groups and that P.M.F. in South Wales appears at a later age than tuberculosis.

(iv) *Prevalence Rates of Tuberculosis*

By prevalence rates of tuberculosis we imply the proportion of persons in some defined group who, either on radiological or bacteriological grounds, are found to have tuberculosis at a specified time. Evidence for such rates must be treated with great care, for there are many sources of error:

(*a*) The group may be highly selected and not representative of the wider group in which we are interested; for instance, miners in hospital and miners receiving pensions are not typical of miners as a whole. For this reason, the work of Williams (1933), Sen (1937), Sokoloff (1936) and Theodos and Gordon (1952) is of limited value.

(*b*) The prevalence of tuberculosis, particularly " healed reinfection type tuberculosis," is related to age, and when comparing the prevalence in different groups the figures must be standardised for age.

(*c*) There is considerable inter- and intra-observer error in X-ray diagnosis of tuberculosis (Yerushalmy *et al.*, 1950) which is probably increased in the presence of pneumoconiosis.

(*d*) It is possible that dust may increase the radio-opacity of tuberculous lesions, and thus cause an artificial increase of tuberculosis prevalence amongst miners when it is assessed radiologically.

(*e*) The radiological diagnosis of tuberculosis in the absence of supporting bacteriological evidence is always open to question.

Three surveys carried out in mining areas in the U.S.A. (Dreesen *et al.*, 1940; Bloomfield *et al.*, 1935; Clarke *et al.*, 1941) showed that the higher the prevalence of pneumoconiosis the higher was the prevalence of tuberculosis. Mann (1951) reported a similar relationship in surveys of British mines carried out by the Pneumoconiosis Research Unit. Mann also attempted to relate the prevalence of tuberculosis to the severity of the associated simple pneumoconiosis, and concluded that with increasing severity of pneumoconiosis the prevalence of tuberculosis increased, becoming manifest as P.M.F. in the higher categories of simple pneumoconiosis. However, his groups were not standardised for age, so that his conclusions are open to the criticism that both the category of pneumoconiosis and the prevalence of tuberculosis may be correlated with age.

The material provided by the Rhondda Fach survey enables us to overcome the difficulty and to carry out a more detailed analysis with standardisation for age. Moreover, the material has the great advantage of providing a nearly complete population of both miners and ex-miners, in a geographically defined area. Colliery populations tend to be selected in that the less fit men tend to leave mining.

All the radiographs of miners and ex-miners in the survey were classified according to the category of simple pneumoconiosis, category 0 indicating absence of simple pneumoconiosis, and categories 1-3 indicating increasing profusion of simple pneumoconiosis according to the International Classification (Cochrane, Davies and Fletcher, 1951). Films with P.M.F. in which the category of simple pneumoconiosis could not be determined (" U.R."), owing to the development of emphysema, were arbitrarily placed in category 3. The number of such films was not great enough to influence the results significantly. Films with localised shadows additional to simple pneumoconiosis were classified as:

1. Inactive tuberculosis—these were films with shadows suggesting healed tuberculous foci.
2. P.M.F. or clinically significant tuberculosis without positive sputum. These were films with shadows suggesting P.M.F. or tuberculosis that was not inactive. These are grouped together, since in many cases it is difficult to differentiate between them and because of the supposition that P.M.F. is an active tuberculous lesion modified by dust.
3. Infectious tuberculosis—these were films with tuberculous shadows or P.M.F. in which sputum or laryngeal swabs were positive for tuberculosis.

All the films were read on two occasions by two observers working together, and a third deciding reading was given to those films in which the first two opinions differed.

Fig. 4 summarises the results in the form of equivalent average prevalence rates. The results in general confirm those of previous workers in that the prevalence of tuberculosis and P.M.F. increases with increasing categories of simple pneumoconiosis. This could be due either to an increased attack rate or a decreased case fatality rate.

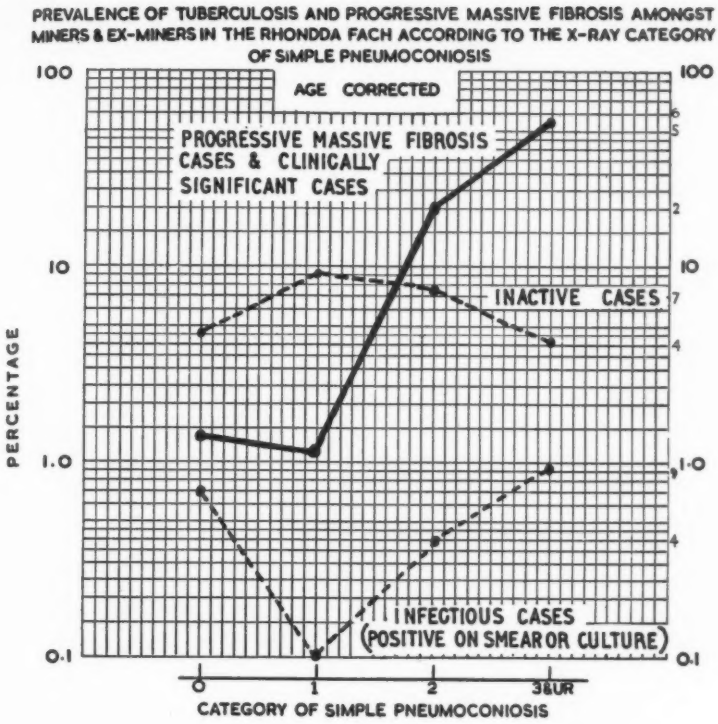

FIG. 4.

As the prognosis is closely related to the sputum findings, some estimate can be obtained of the relative case fatality in the various groups from the prevalence of infectious cases amongst all tuberculous and P.M.F. cases in each group (Table I). This strongly suggests there is a marked fall in case fatality in the pneumoconiotic groups as compared with the " normal " group. The table also shows that the effect is not due to age.

As we already have direct evidence of an increased " attack rate " it seems probable that the increased prevalence is due both to an increased attack rate and a decreased case fatality.

TABLE I.—THE CRUDE AND AGE STANDARDISED PREVALENCE OF INFECTIOUS TUBERCULOSIS AMONGST ALL CASES OF TUBERCULOSIS AND P.M.F. IN FOUR GROUPS OF MINERS (AGED 25-64) WITH DIFFERENT CATEGORIES OF SIMPLE PNEUMOCONIOSIS IN THEIR X-RAYS.

	X-ray category			
	0	1	2	3 *and UR.*
No. of cases of tuberculosis and P.M.F. ..	149	78	231	479
No. of infectious cases	17	1	3	8
Crude prevalence .. .. .. %	11·4	1·3	1·3	1·7
Age standardised prevalence .. %	15·1	0·8	2·5	1·8

We can also use the results shown in Fig. 4 to investigate how these changes in attack rate and case fatality are likely to affect the mortality rate.

The mortality rate will be related to the prevalence of infectious cases in each group (Table II). From this it would appear that with increasing category of simple pneumoconiosis the mortality rate first falls and then rises again, owing to the change in case fatality becoming effective, " earlier " than the change in " attack rate."

TABLE II.—THE AGE STANDARDISED PREVALENCE OF INFECTIOUS TUBERCULOSIS AMONGST GROUPS OF MINERS (AGED 25-64) WITH DIFFERENT CATEGORIES OF SIMPLE PNEUMOCONIOSIS IN THEIR X-RAYS.

	X-ray category			
	0	1	2	3 *and UR.*
No. in group	2,274	756	821	757
No. of infectious cases	17	1	3	8
Age standardised prevalence of infectious cases .. .. %	0·7	0·1	0·4	0·9

Discussion

Hart and Aslett (1942), when they reviewed the subject of tuberculosis amongst coalminers, suggested that there were probably two factors influencing their tuberculosis mortality—" (i) due to occupational environment (or occupational selection), (ii) due to the presence of a pneumoconiosis that has itself developed as a result of the occupation."

It is difficult to exclude occupational selection altogether. Some occupational selection takes place in entering every industry, and some of it inevitably excludes some sufferers from tuberculosis. For instance, those severely ill with tuberculosis at the age of entering the industry will almost certainly be excluded. On the other hand, a large part of the mining industry is located in areas where there are few other industries and both tradition and economic pressure have encouraged sons to follow their fathers to the pits.

The evidence presented here confirms Hart and Aslett's second suggestion that the development of pneumoconiosis affects tuberculosis mortality. We have found that increasing pneumoconiosis category appears to be associated with a decreased case fatality rate and an increased attack rate of tuberculosis with P.M.F. Our evidence thus enables us to suggest one simple explanation for both factors postulated by Hart and Aslett. On the simple hypothesis (Roach, 1953) that the rate of appearance of simple pneumoconiosis in coalminers depends simply upon the concentration of dust to which they are exposed and the time of exposure, miners exposed to relatively low dust concentrations will tend to develop simple pneumoconiosis to the extent of category 1. This will greatly reduce the case fatality of tuberculosis without causing any marked rise in the attack rate. Exposure to higher dust concentrations for the same time, or the same dust concentrations for a longer time, will lead to the development of category 2, and subsequently category 3, simple pneumoconiosis. This will lead to a marked increase in attack rate, and

as a result the mortality rate of the group as a whole will begin to rise again. Thus a little dust exposure gives the beneficial effect of the change in case fatality without the added risk of the rise in the attack rate.

This hypothesis would explain:

1. The favourable tuberculosis mortalities of miners in the eighteenth and nineteenth centuries when mines were shallow and less dusty. There would then be sufficient early pneumoconiosis to have a beneficial effect and little or no advanced pneumoconiosis with P.M.F. to increase the mortality.
2. The relationship between the prevalence of tuberculosis and the prevalence of pneumoconiosis.
3. The variability of the tuberculosis death rates in the various coalfields on a basis of varying dustiness. Two additional reasons may be given supporting the idea that the anthracite area was the dustiest in this country in the earliest part of this century:

   (*a*) The danger of explosions was less owing to the lack of gas, and as a result less attention was paid to ventilation and probably more shot firing was done, and

   (*b*) The certification rates suggest that more pneumoconiosis was found there than in other parts of the coalfields.

4. The higher tuberculosis mortality rates of colliers as opposed to other workers underground on the basis that the latter were getting the " therapeutic " dose while the others had excess.

However, when we try to explain the mechanics of these suggested actions of coal dust, new difficulties appear. It is in general unlikely that the same factor could cause at the same time both a rise in attack rate and a fall in case fatality rate, as one would expect both to be closely related to the resistance of the individual. One obvious way out of this predicament is to suggest that one factor is due to the physical properties of coal dust and the other to its chemical properties. It would, for instance, be very reasonable to suggest that the decreased case fatality rate is due to the ability of coal dust to produce fibrotic lesions (Cummins, 1927; Mann, 1951). This might be a purely physical effect. Coal dust, however, is not a pure substance and contains usually about 1-2 per cent. of free silica, and this is known to increase the attack rate of tuberculosis in animals (Vorwald *et al.*, 1950). It seems therefore possible that the increased attack rate found associated with categories 2 and 3 simple pneumoconiosis might be due to the quantity of free silica in the lung. An attempt was made to investigate this in the following way. All miners and ex-miners with X-rays showing simple pneumoconiosis, categories 2 or 3, with and without early P.M.F. or clinically significant tuberculosis (the former categorised as 2A or 3A), were selected from all the miners and ex-miners X-rayed in the Rhondda Fach survey and were grouped according to the years they had spent exposed to coal dust on the coal-getting shift at the coal face and to stone dust. It can be assumed that the stone dust will have a higher content of free silica than the coal dust. The results are shown in Table III.

TABLE III.—ANALYSIS OF THE INDUSTRIAL HISTORIES OF MINERS AND EX-MINERS LIVING IN THE RHONDDA FACH, AGED BETWEEN 45 AND 50, WHOSE CHEST FILMS SHOWED PNEUMOCONIOSIS CATEGORIES 2, 2A, 3 AND 3A RESPECTIVELY.

X-ray category	*No.*	*Years of exposure to coal dust*	*Years of exposure to stone dust*
2	76	16·3	3·3
2A	23	14·5	2·8
3	46	21·0	2·75
3A	17	18·8	2·9

If silica were an important factor in the etiology of P.M.F., one would have expected to find a higher percentage of stone work in the industrial histories of those with early P.M.F. compared with those without P.M.F., but as is seen no such differences were found. This does not rule out the silica hypothesis, but it is difficult to test it out in other ways.

We clearly cannot come to any definite conclusions at present. We can only suggest that the simplest explanation of the facts available is that coal dust decreases the case fatality of tuberculosis, but that, in larger doses, the attack rate of tuberculosis is increased with a consequent rise in tuberculosis mortality.

It is not suggested that this effect is of immediate therapeutic importance. There is much better evidence proving the effect of streptomycin, P.A.S. and Isoniazid on the case fatality of tuberculosis. It is, however, worth stressing that the statistical evidence in favour of a therapeutic effect of coal is very much better than the evidence produced so far in favour of artificial pneumothorax and pneumoperitoneum.

Summary

A review of the evidence on the prevalence, attack, and mortality rates for tuberculosis in coalminers leads to a simple hypothesis that a little coal dust retained in the lungs has a definite therapeutic effect, whereas larger accumulations increase the attack and mortality rates from tuberculosis.

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INTRAVENOUS P.A.S. IN RELATION TO PULMONARY TUBERCULOTHERAPY

WITH AN ACCOUNT OF 1,145 TRANSFUSIONS

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Drug Resistance in Tuberculosis

The most important stumbling-blocks to the eradication of tuberculosis from the community, at present, are the relapsing and the chronic case. For such patients repeated chemotherapy may be necessary, both for their own well-being and for the prevention of reservoirs of infection in our midst. In the treatment of a community, the immediate recovery of the individual patient can no longer be regarded as final. It is necessary that tubercle bacilli should remain drug sensitive for the patient's sake and for the sake of his infected contacts.

Wilking *et al.* (1952) have reported that of 152 children suffering from tuberculosis, five were resistant to 10γ or more of Streptomycin *before treatment.* A multiplication of this number, as drug-resistant carriers increase, is a prospect we must guard against. It is, therefore, relevant to consider if the fullest proper use of P.A.S. in drug combinations is being made at the present time and to determine whether, in certain cases intolerant of oral P.A.S., an alternative mode of administration should be considered.

P-Amino Salicylic Acid (P.A.S.)

This drug was first synthesised by Seidel and Bittner in 1902, but was rediscovered in 1943 on the basis of studies made by Bernheim (1940, 1941), Lehmann (1946 *a*, *b*, *c*) and Rosdahl. Although initially used alone, P.A.S. is now utilised chiefly for its role in delaying the emergence of bacterial populations of tubercle bacilli predominantly resistant to Streptomycin and Isoniazid. This status, suggested by Bloch *et al.* (1949), has been firmly established by the work of the Medical Research Council (Daniels and Hill, 1952; M.R.C. 1953). It is likely that P.A.S. will occupy this place in treatment until a new weapon appears which can be administered alone without breeding resistant tubercle bacilli.

Toxicity of P.A.S.

Generally speaking, P.A.S. is regarded as a drug of low toxicity, but in 1951 Tempel *et al.* reported that when 12 gm. of P.A.S. daily were given with 1 gm. of Streptomycin, 57·5 per cent. of their patients complained of toxic symptoms. At present the figure would be very much less, but there is no doubt that side effects often occur. Overwhelmingly, symptoms are gastro-intestinal in site, and nausea, diarrhœa, anorexia, vomiting and epigastric pain are

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commonplace during oral P.A.S. therapy. Lacking seriousness though they do, these complaints make the patient miserable, interfere with his food intake and often force the physician to modify his treatment plan.

Rarely other complications may occur:

(i) Drug sensitivity: drug fever, exanthemata, angioneurotic œdema, hay fever, asthma (Gerrits, 1951), Löffler's syndrome (Morandi *et al.*, 1951; Warring, 1952), meningism (Bridge, 1951).
(ii) Headache (Warring, 1952).
(iii) Liver damage, varying from toxic jaundice to acute atrophy with death (McManis and Mira, 1951; Muri, 1952; Thomas, 1952).
(iv) Transient lymphadenopathy (Warring).
(v) Granulopenia (Warring) and aplastic anæmia (Walters, 1953).
(vi) A syndrome of burning eyes, lachrymation and conjunctival injection (Warring).
(vii) Polyneuritis (Brun, 1950).
(viii) A reaction resembling infectious mononucleosis (Warring).
(ix) Hypokalæmia and hypocalcæmia (Cayley, 1950; Jones and Leggatt, 1953).
(x) Reversible urinary changes: increased erythrocyte and leucocyte content, hyaline and granular casts (Hug, 1949). Temporary anuria (Mann, 1953).
(xi) Hypoprothrombinæmia (Gundersen, 1951) and menorrhagia (Levy, 1952).
(xii) Toxic psychosis (Pugh, 1952).
(xiii) Reversible myxœdema (Komrower, 1951; Clausen, 1951; Hamilton, 1953).
(xiv) Skin sensitivity to sunshine (Bunger, 1951).
(xv) Hæmolytic anæmia responding to transfusion (Janet, 1950).

In some cases, several complications occur in one patient, but conversely extraordinary tolerance to P.A.S. may be encountered. Zivy (1952) has instanced two cases who could tolerate 60 gm. and 40-50 gm. daily *per os* without complaint.

Dosage

Although *in vitro* experiments have shown that low concentrations of P.A.S. are effective against the tubercle bacillus, it is not surprising to find that in practice high serum levels have been recommended. The natural defence mechanism of the lung against tuberculosis can be expected to place a barrier between the blood stream and the diseased focus. Daniels and Hill have provided convincing evidence in favour of high dosage. They found that a daily dose of 5-10 gm. of P.A.S. with 1 gm. of Streptomycin allowed 21 per cent. of sputum-positive cases to become highly Streptomycin resistant after four months, whilst of patients receiving 20 gm., 4 per cent. became resistant.

Despite the evidence in favour of high dosage, it is common practice to use less. Mount and Ferebee (1952) in a large trial (526 patients) used 10-12 gm. P.A.S. daily. Israel (1951 *a* and *b*) has stated that although high dosage has been recommended, most American workers find that they can give only 12 gm.

and instances cases where 8 gm. cannot be tolerated. Paraf and Fouquet (1951 *a*) have quoted authors in France and abroad who use only 8-10 gm. daily.

The literature is full of such evidence and it seems clear that gastro-intestinal side effects often tie the hands of physicians who would give larger doses. Since these symptoms are of local rather than central origin, various methods of overcoming gastric and intestinal irritation have been used and these will now be mentioned, since they help present intravenous administration in proper perspective in relation to P.A.S. tuberculo-therapy as a whole.

There are three principal methods—viz., variation in drug presentation, administration of drugs which interfere with P.A.S. detoxication, and parenteral administration.

(*a*) *Variations in the Presentation of P.A.S.*

Purification.—Earlier, there was undoubted confusion about the physical properties of the preparations employed. Many reported toxic symptoms were due to *m*-amino phenol, a product of P.A.S. carboxylation. Purification was the first logical step in eliminating undesirable side effects.

Alteration of the Physical State.—The use of flavoured vehicles, cachets, etc., encourages the patient with minor symptoms but does not help the real sufferer. Certain preparations have been accused of lessening symptoms by causing incomplete or irregular absorption.

Preparation of Chemical Derivatives.—Since the acidic properties of P.A.S. are responsible for some of the gastric symptoms (Boger and Pitts, 1950; Forattini and Selmi, 1951), the preparation of the sodium and calcium salts was undertaken. Whilst it is common experience that Na P.A.S. is better tolerated than P.A.S. (acid), Russell (1952) has shown that over 50 per cent. of patients who have symptoms with Na P.A.S. are symptom-free when given calcium P.A.S. (When considering the dosage of derivatives, it is important to understand that 100 gm. P.A.S. acid = 111·8 gm. Na P.A.S. = 137·gm. crystalline Na P.A.S. = 112·4 gm. Ca P.A.S.).

(*b*) *Drugs which interfere with P.A.S. detoxication.*

Three preparations have been used to inhibit the enzyme system which conjugates P.A.S. with glycine in the body. Such interference with P.A.S. breakdown means high serum levels with normal doses and therapeutic levels with non-irritant doses.

Benemid, whilst itself of low toxicity, when used with P.A.S. may cause the symptoms one seeks to avoid (Wilhelmi and Sanz, 1952; Crofton *et al.*, 1953). But for this, Benemid might be a drug of choice, since 2 gm. per day allow a reduction of P.A.S. intake by 30-40 per cent.

Caronamid has also been discarded because of toxicity.

Irgapyrin has been recommended in a dose of 5 c.c. daily. Regli and Pulver (1952) noted an increase in P.A.S. serum concentrations of 66 per cent. when using this drug and experienced no side effects. Despite this report, it seems unlikely that a preparation containing amidopyrine would meet general acceptance in this country for reasons cogently stated by Discombe (1952).

(*c*) *Parenteral Administration of P.A.S.*

Rectal administration.—Rieber *et al.* (1951 *a*) used this method but were unable to obtain serum concentrations in excess of 7·5 mg. per cent., whilst in most cases the value was less than 5 per cent. Difficulty was encountered in persuading patients to retain enemas, and in a later communication (1951 *b*) it was stated that simultaneous Benemid medication did not result in therapeutically effective serum levels.

Zivy reports that P.A.S. suppositories of more than 3-5 gm. daily are not tolerated.

Bronchial administration in nebulised solution for inhalation (Vonkennel and Worth, 1951) has been attempted and discarded as inefficient and unsuitable.

The subcutaneous route was used by Fisher *et al.* (1951) who administered a solution containing Hyaluronidase. By the drip method, they gave 5 gm. of P.A.S. in two hours and attained a peak serum level of 7·8 mg. per cent. Burning and swelling occurred locally but was not severe. Later workers have given larger doses of isotonic P.A.S. solutions, using Procaine to minimise the discomfort.

Intravenous administration.—This method presents various advantages over all other routes where the patient is intolerant of oral P.A.S. in adequate dosage.

(i) There is no unpleasant local irritant effect on the gastro-intestinal tract.
(ii) There is not the discomfort of the rectal or subcutaneous route.
(iii) Mal-absorption is avoided and the rate and quantity administered can be regulated precisely.
(iv) A therapeutically efficient serum level is obtained.

The remainder of this article is concerned exclusively with this method.

Historical

Lehmann (1946 *a*) first attempted to give P.A.S. intravenously, but was deterred by the thrombophlebitis which occurred at the site of the injection. In 1948 Paraf *et al.* began their studies and the continuing enthusiasm of these workers has been a source of inspiration to many others. In 1949 Paraf described how he had overcome the results of local irritation by using Heparin in the transfusion fluid. In the same year Barclay sought to overcome the sclerotic properties by careful adjustment of *p*H and sterilisation by Seitz filtration. He was able to treat patients daily for six weeks with this solution.

Following this, many others elaborated methods of giving P.A.S. intravenously (Toulou and Pellerat, 1950; Camparotti, 1950; Cocci, 1949; Amberg, 1951), and it was found that 3-4 hour transfusions gave results which, without disadvantage, equalled the 24-hour transfusions.

In 1950 Löffler and Moeschelin described the ease with which 40 gm. of Na P.A.S. daily could be given instead of a previous maximum of 12-14 gm. by mouth. In the same paper they commented on a case of Streptomycin-resistant tuberculous meningitis which responded to intravenous P.A.S. In 1951 Regli and Stäubli reported a personal experience of 2,200 transfusions and again mentioned how 40 gm. daily could be given, stressing that 15 gm. *per os* was the usual maximum in their practice. These workers felt that intra-

venously administered P.A.S. in sufficient dosage equalled Streptomycin. Since this time intravenous administration of P.A.S. has become fairly general in Continental clinics.

Toxicity

Levy, in a review of the subject, has remarked that intravenous P.A.S. is remarkably well tolerated, and this view is echoed by many others. Complications which have been encountered are listed:

(i) Shivering due to impure solutions.
(ii) Thrombophlebitis, seldom widespread and usually localised to the needle site.
(iii) Mild gastro-intestinal disturbances arising only when the drug is given too quickly and the serum level exceeds 40 mg. per cent. (Barclay, Amberg, 1951).
(iv) Adynamia variously postulated as due to potassium or calcium deficiency.
(v) Sensitivity reactions—*e.g.*, drug fever, urticaria, conjunctivitis and facial œdema (Löffler and Moeschelin, Regli and Stäubli).
(vi) Possible aggravation of diabetes mellitus (Paraf *et al.*, 1952 *b*).
(vii) Microscopical hæmaturia (Löffler and Moeschelin).
(viii) Reduction of lymphocyte and eosinophil count (Favez, 1952).
(ix) Lowering of prothrombin time (Desbordes and Bory, 1952; Barclay).
(x) Giddiness and headache (Amberg, Steinlin and Wilhelmi, 1952) with transfusions of less than three hours' duration.

Fouquet (1952) has stated that children easily tolerate intravenous P.A.S. and describes cases treated with as many as ninety daily injections.

There is no evidence to suggest that the intravenous route protects patients against the systemic toxic effects of P.A.S., but there is decided agreement that gastro-intestinal disturbances are reduced to a minimum.

Dosage

Whilst earlier practice was to give 30-40 gm. daily, experience has shown that the same effect can be obtained with smaller quantities. Paraf now gives 15 gm. daily and doses of this order are in general use. Bearing in mind that 14-15 gm. of P.A.S. by mouth give a serum level of 5-10 mg. per cent. (Zivy, collating evidence of twelve authors), it is satisfactory to find that the same dose administered intravenously in 3-4 hours gives levels of over 40 mg. per cent. at 2 hours, 5 mg. per cent. at 12 hours at occasional levels of 3 mg. per cent. at 24 hours (Paraf, 1952 *b*). The value of high serum levels in crossing the meningeal barrier is certain (Desbordes and Bory, Paraf, 1952 *a*) and it is reasonable to assume that a similar crossing of natural tissue barriers occurs in lung disease. Where an initial high level is not maintained throughout the twenty-four hours, it should be borne in mind that experience with other drugs—*e.g.*, Streptomycin and Penicillin—has shown that peak levels are more important than moderate sustained levels.

Apart from any special therapeutic effect, it is clear that intravenous doses of 15 gm. daily are efficient in preventing the emergence of Streptomycin-

resistant strains when used in combination with 1 gm. of Streptomycin daily. Duroux and Coletsos (1951) instance 67 grave cases treated for 150-200 days in this manner and report that, after six months, Streptomycin resistance was increased in less than 5 per cent. of cases.

The Present Series

Twenty-seven cases of pulmonary tuberculosis treated with 1,145 intravenous P.A.S. transfusions are described. The type of case treated is that ordinarily selected for chemotherapy and does not represent a special group. Since it is intended to show how the gastro-intestinal effects of P.A.S. may be reduced by using the intravenous route, irrelevant details are excluded and only symptoms of toxicity are reported in full. In fact, whether P.A.S. was used alone or in combination, the results were of the same excellent nature that one expects from any form of effective chemotherapy.

The inclusion of 7 cases treated by P.A.S. alone must not be regarded as detracting from the general rule that P.A.S. should be given in combination with another drug where possible. Likewise, present conclusions should not be drawn from the fact that, in this series, a trial of treatment on alternate days was made in 23 cases. Until further evidence is available it should be assumed that in general transfusions should be given daily.

Practical Details

A freshly prepared 4·8-5 per cent. solution of crystalline Na P.A.S. (24-25 gm. in 500 c.c.) was used. This dose is equivalent to 17·5-18 gm. of P.A.S. (acid). The solution contained added potassium salts aimed at reducing the risk of hypokalæmia and the *p*H was adjusted to 7·5-8. This solution, which was not isotonic, was subjected to cold sterilisation using a Seitz filter.

Transfusions were always given in the morning after a normal breakfast and the time of administration varied from $2\frac{1}{2}$-$3\frac{1}{2}$ hours according to tolerance. Some cases received Vitamin K (Roche) 1 c.c. in the transfusion. A Record size 8-12 needle was used, and because of the risk of accident or poor technique the principal named veins were avoided during the earlier part of treatment. It was the practice to alternate between available veins. In all respects, the technique was as for saline or plasma transfusion by the " drip " method.

Results

During treatment, all patients were carefully questioned about possible side-effects and every complaint has been listed. Symptoms spontaneously complained of are indicated in the table by an asterisk, whilst those revealed by closer questioning are unmarked.

Gastro-intestinal symptoms were experienced by two patients only (6 and 19). In Case 6 this was a mild temporary nausea only, which allowed the patient to eat a good tea and supper. Case 19, who had previously been quite intolerant of oral P.A.S. because of severe abdominal pain, experienced only mild diarrhœa with the intravenous preparation. Case 8, with a similar history of P.A.S. intolerance had no symptoms.

Venous thrombosis was unremarkable. Local reaction seldom occurred and

was usually to be attributed to extravenous injection. Two patients only (Cases 3 and 15), both seriously ill with empyema and broncho-pleural fistula, showed unusual predisposition to thrombophlebitis, but in neither was there cause to stop using arm veins.

Fever occurred in 2 cases. Case 1 had fever of 101° F. for seven days at the commencement of intravenous therapy, but this could be attributed to a recent bronchogenic spread for which the treatment was prescribed. Case 20 had a fever "spike" of 101° F. on two occasions following transfusion. No case of drug fever was encountered.

Tiredness experienced regularly by four patients (7, 17, 19, 21) was ascribed to the P.A.S. Two of these patients slept regularly during transfusions.

Eye symptoms occurred in four patients. Case 16 experienced mild photophobia of half-hour duration at the end of the transfusion, whilst Case 13 suffered similarly and developed allergic kerato-conjunctivitis two weeks after treatment was discontinued. This unfortunate complication cleared rapidly with specialist treatment. Three patients, including Case 13, suffered difficulty with adaptation for near vision towards the end of each transfusion, but this minor inconvenience disappeared speedily when the transfusion ended.

Vaso-motor symptoms.—Two patients had visibly flushed faces for the last hour of transfusion.

Vestibular symptoms occurred in two patients who complained of a transitory subjective unsteadiness when sitting up after treatment. In one case (14) this happened on one occasion only and resulted from accidental injection over a period of two hours.

Headache.—In one patient the connection of this symptom with treatment was inconclusive.

Anal soreness troubled one male patient. Here also the relevance of this was in doubt.

Abdominal pain identical with dysmenorrhœa troubled Case 22. This was not severe and commenced during the last hour of treatment, lasting for one and a half hours.

Tightness in the chest was remarked upon as a very insignificant symptom by one patient.

Neuralgic pain, constant in type, distributed over the right maxillary and mandibular divisions of the trigeminal nerve, was encountered in one patient when the transfusion time was less than three and a half hours.

Granulopenia was observed in Case 19. The absolute polymorphonuclear leucocyte count fell from 63 to 41 per cent. during treatment, whilst a corresponding increase in lymphocytes occurred.

Reference to the table shows that only seven patients spontaneously complained of symptoms (two cases of venous thrombosis, three with eye symptoms, one with facial pain and one who felt tired). None of these patients regarded their symptoms as more than minor inconveniences and none agreed that they would abandon intravenous treatment if given the choice. Rather surprisingly, only one patient (18) complained that she disliked "the needle." Most patients were familiar with the possible gastro-intestinal side effects of oral P.A.S. as a result of personal experience (17 patients) or hearsay and were quite glad to take P.A.S. intravenously. A common remark was, "It's nice to

get it over and done with in the morning and not have to face P.A.S. tablets all through the day."

The length of treatment appeared to have no effect upon the incidence of symptoms, and without any biochemical evidence it would seem that no harmful changes in blood chemistry can have taken place. Fifteen patients gained weight and seven lost during treatment. Serious weight loss occurred in two patients, of whom one was dieting deliberately and the other was very gravely ill.

Discussion

The present investigation tends to confirm the impression of other workers that the incidence of gastro-intestinal symptoms during the course of P.A.S. therapy is small when the intravenous route is used. With a dosage of 20 gm. of anhydrous Na P.A.S. no disturbing gut symptoms were encountered and on no occasion was adjustment of dosage called for. The rapid ($2\frac{1}{2}$-$3\frac{1}{2}$ hours) transfusion method, besides providing additional therapeutic advantages in the form of high serum concentrations of P.A.S., allows any patient who is troubled with anorexia or nausea of central origin (1 case in this series) to recover appetite and eat normally later in the day. Administration of P.A.S. to patients too ill to take it by mouth (2 cases) was made possible by the intravenous method.

Of other symptoms unconnected with the intestinal tract, little needs to be said. It is evident that refinement in the methods of preparing P.A.S. solutions, together with the discarding of twenty-four-hour transfusions has resulted in venous thrombosis becoming much less of a problem (see Carter, 1952). However, it does seem that gravely ill patients are still open to this complication. Difficulty with visual adaptation, tightness in the chest and vestibular symptoms are not peculiar to P.A.S. therapy and may be encountered whenever large quantities of fluid are introduced into the body by the intravenous route. The neuralgic pain encountered by Case 22 is the only symptom for which no precedent or explanation can be put forward. Unfortunately no biochemical investigations were carried out on the patients who complained of tiredness. This symptom is probably identical with the adynamia referred to by Levy.

On examining the data presented, one has the impression that, in the dosage used, patients weighing less than $8\frac{1}{2}$ stones (55 Kg.) experience symptoms more readily than heavier patients. In general, it was found that these patients asked for the transfusion to be run more slowly. The well-nourished men in the series admitted ability to "speed up" the drip on occasion, and as recorded, Case 4 medicated himself in two hours on one occasion.

If due consideration is given to the "inundation" of the patient which takes place during the period of the transfusion, with P.A.S. serum levels of about 40 mg. per cent. this record of 27 patients so treated can be said to speak favourably for this route of administration as a method of reducing the gastro-intestinal complications of P.A.S. therapy. On the other hand, there is no reason to suppose that intravenous P.A.S. has any special property of preventing the systemic side effects of P.A.S., as instanced by the occurrence of fever, headache and allergic kerato-conjunctivitis in the present series. Nor can any claim be made that this method is more efficient than oral P.A.S. in preventing

TABLE

Case	*Age*	*Weight*	*Details of treatment*	*Outcome*	*Wt. change*	*Toxic symptoms*
1	23	7 st. 7 lb.	58 transfusions (alternate days) with 250 mg. Isoniazid	Favourable	Gain 6 lb.	Fever at commencement of therapy (see text).
2	33	11 st. 3 lb.	50 transfusions (daily) with 300 mg. Isoniazid	Favourable	Constant	None.
3	39	6 st. 9 lb.	29 transfusions (alternate days)	Inconclusive	Constant	*Venous thrombosis.
4	22	11 st. 10 lb.	40 transfusions (daily) with 1 gm. Streptomycin and 300 mg. Isoniazid	Favourable	Gain 2 lb.	Unsteady feeling in head when transfusion given in less than two hours.
5	32	9 st. 1 lb.	51 transfusions (alternate days) with 1 gm. Streptomycin daily	Favourable	Gain 15 lb.	None.
6	20	8 st. 11 lb.	36 transfusions (alternate days)	Favourable	Gain 3½ lb.	A little nausea for one and a half hours at end of transfusion.
7	28	7 st. 4 lb.	46 transfusions (alternate days)	Favourable	Gain 3½ lb.	Tiredness on day of transfusion.
8	46	8 st. 9 lb.	20 transfusions (alternate days) with 1 gm. Streptomycin daily	Inconclusive	Gain 1lb.	None.
9	36	8 st. 13 lb.	60 transfusions (alternate days) with 250 mg. Isoniazid daily	Inconclusive	Gain 3½ lb.	None.
10	42	8 st. 1 lb.	40 transfusions (alternate days) with 250 mg. Isoniazid	Favourable	Gain 6 lb.	None.
11	24	8 st. 1 lb.	57 transfusions (alternate days)	Favourable	Loss 2 lb.	*Eyes felt swollen and reading was an effort for two hours after transfusion.
12	22	8 st. 6 lb.	50 transfusions (alternate days) with 300 mg. Isoniazid	Favourable	Constant	*Eye symptoms identical with Case 11.
13	34	6 st. 13 lb.	66 transfusions (alternate days) with 300 mg. Isoniazid	Favourable	Constant	*Allergic kerato-conjunctivitis two weeks after cessation of treatment. Eye symptoms identical with Cases 11 and 12.
14	20	11 st. 4 lb.	23 transfusions (daily)	Inconclusive	Loss 6 lb.	Anal soreness.
15	23	10 st. 10 lb.	36 transfusions (daily) with 1 gm. Streptomycin	Favourable	Loss	*Venous thrombosis.

Case	*Age*	*Weight*	*Details of treatment*	*Outcome*	*Wt. change*	*Toxic symptoms*
16	21	10 st. 1 lb.	35 transfusions (alternate days) with 1 gm. Streptomycin twice weekly	Favourable	Loss 1 lb.	Slight photophobia for half an hour after transfusion. Occasional slight tightness in chest during last hour of transfusion.
17	31	10 st. 7 lb.	57 transfusions (alternate days) with 1 gm. Streptomycin twice weekly	Favourable	Gain 4½ lb.	Always hot and flushed for last hour of transfusion. Occasional headache. Invariably slept after transfusion.
18	22	7 st. 10 lb.	50 transfusions (alternate days)	Favourable	Loss 1 lb.	Occasional pain identical with dysmenorrhœa for last hour of transfusion and continuing for half an hour after transfusion.
19	32	8 st. 3 lb.	62 transfusions (alternate days) with 300 mg. Isoniazid daily and 1 gm. Streptomycin twice weekly	Favourable	Gain 2 lb.	Some discomfort after food and occasional heartburn. Mild diarrhœa and sleepiness after transfusion. Granulopenia.
20	32	9 st. 10 lb.	61 transfusions (alternate days) with 300 mg. Isoniazid	Favourable	Gain 2 lb.	Subjective unsteadiness and visibly flushed face after transfusion. Temperature "spike" of 101° F. on two occasions.
21	28	7 st. 3 lb.	45 transfusions (alternate days) with 300 mg. Isoniazid	Favourable	Loss 1 lb.	Tiredness for last three transfusions only.
22	34	7 st. 9 lb.	24 transfusions (alternate days)	Inconclusive	Gain 4 lb.	*Neuralgic pain in right side of face during rapid transfusion.
23	26	8 st. 10 lb.	27 transfusions (alternate days) with 250 mg. Isoniazid	Favourable	Gain 1½ lb.	None.
24	32	9 st. 11 lb.	32 transfusions (alternate days)	Inconclusive	Gain ½ lb.	None.
25	28	10 st. 9 lb.	26 transfusions (alternate days) with 300 mg. Isoniazid	Favourable	Gain 1 lb.	None.
26	22	10 st. 7 lb.	14 transfusions (alternate days)	Inconclusive	Constant	None.
27	39	13 st. 12 lb.	50 transfusions (alternate days) with 300 mg. Isoniazid and 1 gm. Streptomycin thrice weekly	Inconclusive	Loss 12 lb.	None.

* Indicates symptoms spontaneously complained of.

the emergence of Streptomycin or Isoniazid resistant strains, *when the full dose can be taken without distress.*

It is not within the scope of this article to discuss the application of intravenous therapy to the treatment of tuberculous meningitis or to cases of pulmonary tuberculosis resistant to other chemotherapeutic agents, but it would seem that further reports on a series of this nature would be valuable.

Summary

An account of P.A.S. in tuberculo-therapy is given, with a review of toxicity.

Attention is drawn to the way in which P.A.S., in combination with Streptomycin, is sometimes given in inadequate dosage as a result of gastro-intestinal side effects experienced by the patient. The danger of drug-resistant tubercle bacilli emerging is stressed.

Methods of overcoming the local irritant effects of P.A.S. are discussed briefly and an account of the intravenous method of administration is given, together with a personal experience of 1,145 transfusions in 27 cases.

It is concluded that the intravenous administration of P.A.S. should be tried when full dosage is not possible by mouth, since there is evidence that gastro-intestinal symptoms are minimised.

All the patients described in this series were treated at the Sanatorium Park and Sanatorium Angleterre, Davos. I am most grateful to Dr. F. Charles and Dr. A. Walser, the Superintendents, for introducing me to intravenous treatment as employed at these sanatoria.

I am indebted to Sir John Charles, Chief Medical Officer, Ministry of Health, for permission to publish, and to Dr. James Maxwell, who first suggested that I write this report.

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STREPTOMYCIN REACTIONS

THEIR CHARACTERISTIC FEATURES, INCIDENCE, ETIOLOGY AND MEANS OF PREVENTION

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With the increasing use of long-term chemotherapy in the treatment of pulmonary tuberculosis, it is becoming apparent that a relatively large number of patients experience unpleasant symptoms within a few hours of an intramuscular injection of Streptomycin. Although in the majority of cases these " reactions " are of a trivial nature, in some they are extremely unpleasant and may even render the patient incapable of work. Because of their seriousness sometimes an investigation has been made into the etiology and the means of preventing these reactions to Streptomycin.

Material

One hundred and fifty adult patients in the Brompton Hospital Sanatorium, 75 males and 75 females, who were having, or had had, Streptomycin in the treatment of pulmonary tuberculosis, were questioned as to whether the drug had affected them in any way. There was no selection of patients and leading questions were deliberately avoided as much as possible. The average age of the patients in this investigation was 30·39 years, the youngest being 16 and the oldest 56 years of age.

Toxic Symptoms and their Incidence

The various unpleasant symptoms encountered were tingling paræsthesiæ in and around the mouth, vertigo, ataxia, headaches, lassitude, feelings of " muzziness in the head " and difficulty in visual accommodation.

In the total of 150 patients treated with Streptomycin, 55 (36 per cent.) complained of toxic symptoms on the day of injection. The frequency with which the different toxic symptoms occurred is shown in the table below.

Symptom	*Number of patients affected*
Paræsthesiæ in and around the mouth ..	41
Lassitude and " muzziness in the head "	11
Vertigo and ataxia	10
Headaches	10
Difficulty in visual accommodation ..	7

The reactions have been classified arbitrarily into three degrees of severity, + indicating a trivial reaction, ++ a definitely unpleasant reaction, and +++ a reaction severe enough to interrupt the patient's daily routine.

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Number of patients affected		*Severity of reaction*		
		+	++	+++
Males	21	13	4	4
Females	34	23	10	1

Some patients with trivial reactions were not always affected by every injection of Streptomycin, but the remainder with moderate or severe symptoms generally experienced reactions after every injection.

Symptoms usually began between one and three hours after the injection of Streptomycin and some or all persisted from one to twenty-four hours.

Eight of the 19 patients with moderate or severe reactions complained that their symptoms were made appreciably worse by exercise and relieved, partially or completely, by rest. It was decided, therefore, to investigate the effect of exercise on the rate of absorption of Streptomycin from an intramuscular injection. All 25 patients in whom this investigation was carried out were being treated with intermittent Streptomycin, either twice or thrice weekly, in conjunction with daily para-aminosalicylic acid (Gm. 16 to 20) or isonicotinic acid hydrazide (mgm. 200).

Investigation

The serum Streptomycin levels at rest and during exercise were determined on consecutive days for each of 25 patients. On the first day the patient rested in bed whilst venous blood samples were taken immediately before, and half an hour, one and a half hours and three hours after an intramuscular injection of Streptomycin sulphate G. 1 into the buttock. The same procedure was repeated on the following day, but on this occasion the patient was ambulant and took walking exercise in the grounds of the sanatorium.

In addition to the estimation of the rate of absorption of Streptomycin, the rate of excretion in the urine at rest and during activity has also been determined. The latter investigation was considered necessary in order to demonstrate whether there was any difference in the rate of excretion of Streptomycin during rest and activity, since a gross alteration in renal function would obviously have influenced the blood levels.

The technique of this investigation was similar to that used for the estimation of the Streptomycin blood levels, except that the urine specimens were obtained at hourly intervals and special precautions taken to ensure that the fluid intake was the same on the two days of the test.

The assays of Streptomycin in the blood and urine samples were all performed at the Brompton Hospital Bacteriology Laboratory by the agar diffusion method of Mitchison and Spicer (1949).

Results

In 21 of the 25 cases investigated the blood levels of Streptomycin were found to be highest during activity; only in the 4 remaining cases were the resting levels highest.

The graph below shows the mean results of this investigation. It will be seen that the mean serum Streptomycin levels during activity were consistently higher than those at rest, the greatest difference being at half an hour when the Streptomycin level during activity was approximately 50 per cent. greater than the corresponding resting level. At one and a half hours there was a difference of 20 per cent., and at three hours 10 per cent.

The complete results obtained in this investigation have been submitted to a statistical analysis, and this confirms that the difference between the mean active and resting blood Streptomycin levels is significant at the half-hour point (P less than 0·05), but not at the one and a half and three hour points. Although the differences at one and a half and three hours are not large enough to be statistically significant, they are nevertheless not inconsistent, since they are both in the same direction as that at half an hour.

In 5 patients with moderate or severe reactions, which were abrupt in onset, it was possible to relate the time of onset of their reactions to the blood Streptomycin level. It will be seen from the graphs of these patients which are shown below that the onset of a reaction corresponded closely with the peak blood Streptomycin level. Four patients had reactions during activity only, whilst the fifth, although he complained of reactions during both phases of the test, was less severely affected when resting.

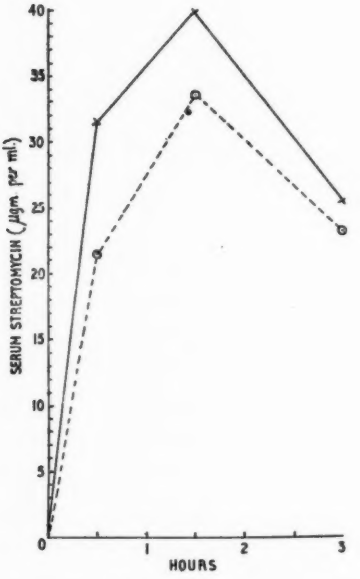

FIG. 1.—Mean serum-streptomycin levels of 25 patients at rest and during exercise after streptomycin G. 1 intramuscularly: continuous line, during exercise; interrupted line, at rest. Mean age of patients, 29·2 years; mean weight, 63·3 kilogrammes.

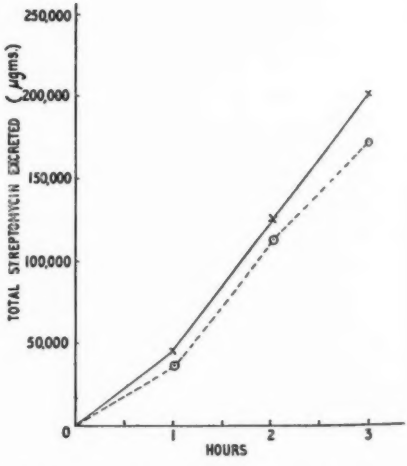

FIG. 2.—Excretion of streptomycin in the urine (cumulative) during rest and exercise after streptomycin G. 1 intramuscularly: continuous line, during exercise; interrupted line, at rest. Mean of 25 patients: mean age, 30·2 years; mean weight, 72·7 kilogrammes.

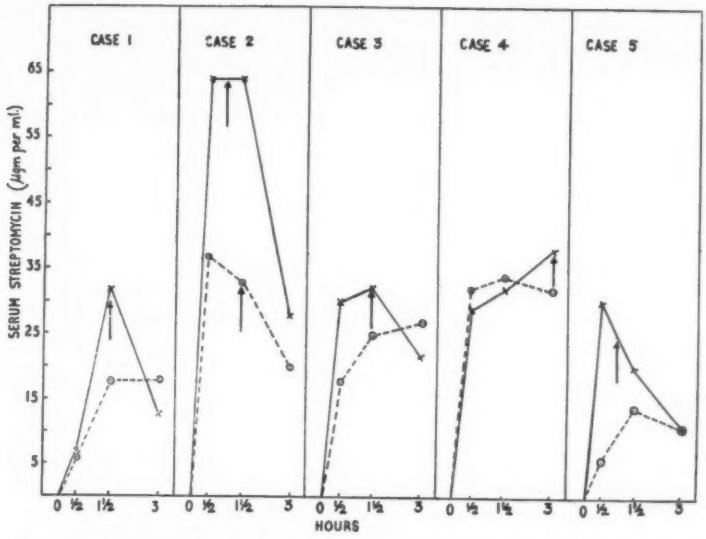

FIG. 3.—Serum-streptomycin levels of 5 patients at rest and during exercise after streptomycin G. 1 intramuscularly: continuous line, during exercise; interrupted line, at rest; arrows mark onset of reactions.

The rate of excretion of Streptomycin in the urine during rest and activity has also been determined in 25 patients. The mean results from this investigation, shown graphically below, indicate that activity caused no significant change in the rate of excretion of Streptomycin.

Treatment

It is the common practice in sanatoria to give patients their injections of Streptomycin first thing in the morning, before the start of the day's activity. But because rest after the injection appeared to diminish or prevent subsequent reactions, 10 patients who experienced moderate or severe reactions were given their Streptomycin at night, shortly after retiring to bed. With this regimen, 7 patients obtained complete relief from symptoms and 2 were considerably improved. The remaining patient (Case No. 2) complained that he was not improved because he was left with a headache the following morning. It will be seen from the graphs that this patient had reactions during both the active and resting stages of the investigation. It was not to be expected, therefore, that he would gain complete relief from the new regimen.

Headaches could usually be relieved with small doses of aspirin (gr. 10). Antihistamines had no obvious beneficial effects on the reactions.

Discussion and Review of the Literature

There is no literature relating to transient toxic reactions following intramuscular Streptomycin as described in this paper, except that by Riches

(1954), which reports the preliminary findings in the present investigation. In addition, no reference could be found to a satisfactorily controlled investigation of the influence of exercise on the rate of absorption of a drug injected intramuscularly.

It is perhaps surprising that unpleasant symptoms occurring as frequently as in this series should not have attracted more attention. In many cases, of course, the symptoms are only trivial, but even if these are ignored there still remains a significant number (12 per cent.) in whom the reactions are of a more serious nature. One can only suppose that in the past, when Streptomysin was usually given in short courses to patients who were confined to bed, the problem caused little concern since the blood Streptomycin level tends to remain lower while resting, and there is consequently less likelihood of reactions occurring. With the present-day tendency to give long-term chemotherapy to ambulant patients, however, these reactions become of more importance, especially if patients are to continue treatment with Streptomycin after returning home and beginning work.

The various types of toxic reactions to Streptomycin which have previously been recorded in the literature by numerous authors (Armstrong *et al.*, 1950; D'Esopo and Steinhaus, 1947; Farrington *et al.*, 1947; Keefer and Hewitt, 1948; and Waksman, 1949), have been classified by McDermott (1947) into five general types: (1) the so-called " histamine " reaction; (2) irritation at the site of injection and on topical application; (3) various manifestations of anaphylaxis such as fever, cutaneous eruptions, blood eosinophilia, etc.; (4) renal irritation, occasionally accompanied by impairment of renal function; and (5) neurological disturbances characterised by vestibular dysfunction and deafness.

The " histamine " reaction is described as being similar to the phenomenon produced by an injection of histamine and consists of flushing, headache and an abrupt fall of blood pressure. It usually occurred soon after an intravenous or intramuscular injection of Streptomycin, but is of little interest now since this type of reaction is not produced by the highly purified Streptomycin which is available for clinical use to-day. There is now general agreement that these reactions were due to contaminating substances which were present in the earlier preparations of Streptomycin. Histamine was implicated since Histaminase-treated Streptomycin would no longer produce reactions in animals.

Although the histamine reaction has a superficial similarity to the transient toxic reactions described in this paper, the flushing and fall of blood pressure, which are characteristic of the histamine reaction only, should help to eliminate confusion.

One other group of reactions in McDermott's classification which has some bearing on the present subject is that containing the neurological disturbances. Two types are described, those with vestibular disturbances, which are relatively common, and those with deafness, which are rare. Both of these complications are typically permanent or very slow in recovery, and occur most commonly in patients having daily Streptomycin in large dosage.

The vertigo complained of by patients in this investigation was of a transient nature, lasting usually not more than one or two hours, and left no permanent

disability as judged by clinical tests. Deafness did not occur. It seems probable that these transient symptoms of vertigo, ataxia and paræsthesiæ are the early manifestations of the neuro-toxic action of Streptomycin which, when the latter is given in large dosage, may lead to permanent damage.

Investigation has shown that the onset of reactions coincides fairly closely with the peak blood Streptomycin level which, in ambulant patients, is usually attained between one and one and a half hours after the injection. Although in this series all reactions began when the serum Streptomycin had risen to something greater than 30 μgm./ml., it seems that the liability to experience reactions depends on the individual, since some patients with blood levels as high as 60 to 90 μgm./ml. had no unpleasant symptoms, whereas another patient with a peak blood level of 32 μgm./ml. was almost incapacitated.

The blood levels of Streptomycin attained after various intramuscular and intravenous doses have been recorded by a number of authors, including Buggs *et al.* (1946), Forgacs *et al.* (1946), Hobson *et al.* (1948), Zini (1950) and Zintel *et al.* (1945). Anderson and Jewell (1945) state that after Streptomycin G. 0·6 intramuscularly a peak level of 12 to 16 μgm./ml. of serum is to be expected between one and two hours after the injection. After an intravenous injection of the same amount the peak blood level occurs within five minutes and is usually between 28 and 40 μgm./ml. of serum. With high intravenous dosage such as this some patients complained of a " peculiar taste " in the mouth, throbbing headaches and flushing of the face. Buggs *et al.* (1946) record even more dramatic effects after Streptomycin G. 0·5 intravenously. Two of their patients complained of a " bad taste " in the mouth, dizziness, respiratory difficulty, and finally became unconscious, whilst others complained of headaches, flushing of the skin and a sensation of fullness in the head. It is difficult to know whether these reactions after intravenous Streptomycin were due to the drug or whether they were the so-called " histamine " reactions due to contaminating substances. It seems very probable that they were due to contaminants, since both Anderson and Buggs were recording observations made prior to 1946 and, therefore, before highly purified specimens of Streptomycin were available.

The average blood levels in adults after Streptomycin G. 1 intramuscularly were found by Buggs *et al.* (1946) to be 25 to 50 μgm./ml. at one hour, 25 to 45 μgm./ml. at two hours and 15 to 25 μgm./ml. at four hours. A similar investigation on children has been carried out by Hunt and Fell (1949). They have shown that the blood Streptomycin level varies with the dose given and that after 6·6 mgm./Kilo body weight of Streptomycin intramuscularly the peak blood level lies between 10 and 24 μgm./ml., and that after 15·4 mgm./Kilo body weight a peak blood level of 25 to 47 μgm./ml. is to be expected. Neither Buggs nor Hunt states whether these figures concern ambulant or bed patients.

The actual blood level found in a patient at any given time after an intramuscular injection of Streptomycin G. 1 is obviously dependent on three main factors—namely, (*a*) the rapidity with which the drug is absorbed from the site of injection, (*b*) the volume of the body fluids in which it is to be distributed, and (*c*) the rate at which it is destroyed or eliminated from the body.

Marshall (1948) has stated that Streptomycin is distributed in the human

body as if it were present in the extra-cellular fluids only. For the ordinary hospital and sanatorium patient, who is not in cardiac or renal failure, it may be assumed that the total extra-cellular fluid remains constant for each individual and, therefore, in the individuals under consideration here, factor (*b*) above may be considered a non-variable for each patient. This leaves only two variable factors which can influence the blood level of Streptomycin—namely, the rate of absorption from the site of injection and the rate of excretion.

The solubility of the drug, the volume and nature of the vehicle in which it is dissolved, and the site of injection, can all obviously affect the speed of absorption of a drug from an intramuscular injection. In the present investigation, however, there were no such variables since all patients were given Streptomycin sulphate G. 1 dissolved in 4 ml. of distilled water, intramuscularly into the upper outer quadrant of the buttock. The only other factor which could possibly influence the speed of absorption of the Streptomycin was, therefore, the activity of the patient. That activity should influence the rate of absorption of a drug given intramuscularly is quite logical, since it is well known that the blood flow through a muscle, and the lymph return from it, are both considerably increased during exercise. It is not unreasonable to suppose, therefore, that Streptomycin given by injection into the leg or buttock will be more quickly absorbed in an ambulant patient than in one who is resting. Although Peacock and Gillespie (1950) made the tentative suggestion that variations in the blood flow through a muscle during rest and activity might influence the speed of absorption of drugs given intramuscularly, they did not prove their hypothesis. In an investigation of the persistence of a therapeutic blood level of Penicillin following the intramuscular injection of Procaine Penicillin with Aluminium monostearate, they found that a therapeutic blood level persisted for six or seven days, or longer, in bed patients, but that in the majority of ambulant patients a therapeutic blood level persisted for five days only. They assumed that this difference in the persistence of an effective blood level was due to a difference in the speed of absorption of the Penicillin and made no reference to possible variations in the rate of excretion. Boger *et al.* (1948) and Emery *et al.* (1949) also observed differences in the persistence of therapeutic blood levels of Penicillin in resting and ambulant patients, but, like Peacock *et al.*, they did not demonstrate that a more rapid absorption of Penicillin occurred in ambulant patients, nor did they investigate the rate of excretion of Penicillin. Kirby *et al.* (1945) found no appreciable differences in the blood levels of Penicillin in ambulant and resting patients twelve hours after an injection of a Penicillin-Beeswax-Peanut oil preparation.

Although the 25 cases in this investigation showed a mean difference of 50 per cent. between the resting and ambulant blood Streptomycin levels at half an hour, it was considered necessary to demonstrate that renal function was unaltered by activity before attributing this difference solely to an alteration in the speed of absorption. Many authorities (Adcock and Hettig, 1946; Anderson and Jewell, 1945; Buggs *et al.*, 1946; Elias and Durso, 1945; Heilman *et al.*, 1945; Herrell and Heilman, 1947; Hewitt, 1947; Marshall, 1948; and Zintel *et al.*, 1945) have shown that in man up to 90 per cent. of a given dose of

Streptomycin is excreted in the urine within twenty-four hours. It is thought that renal excretion of Streptomycin is effected by glomerular filtration only, since Adcock *et al.* (1945) have shown that the plasma clearance of Streptomycin is at the rate of 30 to 80 ml. per minute, which is well within the glomerular filtration rate of 130 ml. per minute (Smith *et al.*, 1938).

Investigation of 25 cases has revealed that although the volume of urine passed was less during activity, the concentration of Streptomycin in it was increased and, on calculation, there was found to be no significant difference in the actual quantities of Streptomycin excreted during rest and activity. It may be concluded, therefore, that the differences in the blood levels of Streptomycin during rest and activity are due solely to a difference in the speed of absorption of the drug from the site of injection.

A number of patients, in whom reactions were severe, have gained relief by resting immediately after their injections of Streptomycin, or by having their Streptomycin last thing at night shortly after retiring to bed. This is presumably due to the more gradual absorption of the Streptomycin and the subsequent slightly lower peak concentration in the blood. For those with severe reactions these methods are obviously justified, but for those with trivial reactions it may be questioned whether it is desirable to introduce a regimen which reduces the blood level of Streptomycin. It is impossible to answer this at present, since the optimum blood Streptomycin level for the treatment of pulmonary tuberculosis is undecided and presumably will vary from case to case, depending on the sensitivity of the organism and the type of disease. Pagel *et al.* (1953) believe that a blood Streptomycin level of 4 μgm./ml. is the minimum concentration necessary to affect bacilli in the tissues. *In vitro* studies by Hinshaw *et al.* (1947) have shown that as little as 0·25 to 1 μgm./ml. of Streptomycin is bacteriostatic for *M. tuberculosis* H.37 Rv, whilst Garrod (1950) has demonstrated *in vitro* that the bactericidal effect of Streptomycin on *M. tuberculosis* H.37 Rv is directly proportional to the concentration of the drug and the duration of exposure. He found that cultures of this organism could be sterilised in eight hours by a solution containing 50 μgm./ml. of Streptomycin, whereas a solution containing 20 μgm./ml. took twenty-four hours to achieve the same result.

Although it is unwise to assume that the actions of a drug *in vivo* are necessarily the same as those *in vitro*, it would appear that in adults Streptomycin G.1 intramuscularly can be expected to give rise to a bactericidal blood level for a few hours and a bacteriostatic level for a longer period. Because the bactericidal level is not maintained for a sufficient length of time to be completely effective, Youmans (1946) and Smith and Waksman (1947) have suggested that the primary action of Streptomycin *in vivo* is bacteriostatic. If this opinion is accepted, it becomes apparent that the difference of 6 μgm./ml. between the mean active and resting peak blood Streptomycin levels is so small as to be therapeutically unimportant. It is justifiable, therefore, to encourage patients to rest after the administration of Streptomycin, if they experience unpleasant reactions, and it is suggested that an adequate period of rest can be assured quite simply by giving the drug in the evening, immediately before the patient retires to bed.

Summary

1. In a series of 150 patients, 55 (36 per cent.) complained of toxic symptoms within a few hours of an intramuscular injection of Streptomycin.

2. The various unpleasant symptoms complained of were circumoral paræsthesiæ, lassitude, "muzziness in the head," vertigo, ataxia, headaches and difficulty in visual accommodation.

3. In a total of 19 patients with severe reactions, 8 complained that their symptoms were made worse by exercise and relieved by rest.

4. Investigation of the blood Streptomycin levels during rest and activity following Streptomycin G. 1 intramuscularly has shown that there is a significant increase in the rate of absorption of the drug during activity.

5. In 7 of 10 patients who normally experienced severe symptoms, complete relief was obtained when Streptomycin was given at night, shortly after retiring to bed. It is suggested that this regimen is an effective method of prophylaxis and should be adopted for patients with severe reactions.

6. The relevant literature has been reviewed and the incidence, etiology and prophylaxis of Streptomycin reactions discussed.

My thanks are due to the Physicians of Brompton Hospital for allowing me to carry out the investigations on their patients. I am especially grateful to Dr. J. L. Livingstone and Dr. A. F. Foster-Carter for encouragement and advice and Mr. Bernard Benjamin, Statistician, for his analysis of the results.

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DIAPHRAGMATIC PNEUMOCELE TERMINATING ARTIFICIAL PNEUMOPERITONEUM TREATMENT

By J. D. Powell David

From the Chest Clinic, Wolverhampton

One of the outstanding features of artificial pneumoperitoneum treatment is the relative infrequency of complications. Among these diaphragmatic pneumocele is something of a rarity. The paucity of literature on this condition emphasises the infrequency of its observation, but this is no true indication of the gravity of its development.

A somewhat similar condition, but to a lesser degree, has been observed at thoracoscopy when a pneumothorax was present in addition to a pneumoperitoneum. Laird (1945) noted vesicles on blebs on the upper surface of the diaphragm at thoracoscopy in 4 patients undergoing combined pneumothorax and pneumoperitoneum treatment. The hemidiaphragm had been paralysed by phrenic operation in each case, and he associated the condition with defects in the diaphragmatic peritoneum and with the fibres of the diaphragm being thinned and stretched as a result of paralysis. He was inclined to connect this condition with the complication of spontaneous pneumothorax developing during pneumoperitoneum treatment. Cope, in a personal communication to Ross and Faber (1951), noted a large bleb on the diaphragm at thoracoscopy in a patient with a spontaneous pneumothorax complicating pneumoperitoneum treatment. This bleb varied in size with each respiration, enlarging whenever the intraperitoneal pressure increased. Phrenic paralysis was not present.

This condition has been identified radiologically in the first instance by Repa and Jacobson (1951) who noted a ring shadow 4·5 by 3 cm. at the right base in a patient undergoing pneumoperitoneum treatment. They assumed it was a " large emphysematous bleb." Sixteen days later and 13 days after the last refill the patient developed a large positive pressure pneumothorax. Return to hospital was necessary for immediate removal of air from the pneumothorax. The ring shadow had by then disappeared. Thoracoscopy showed a 1 cm. rent in the diaphragm in addition to a pedunculated cyst-like mass. A rupture of the " emphysematous bleb " or a similar structure was suspected and these radiological appearances should serve as a warning of imminent diaphragmatic rupture.

Case Report

M.L., female, aged 25 years, married with two children. She was found to have pulmonary tuberculosis with positive sputum in November 1952. Dense infiltration was present in both upper zones with cavitation in the right upper zone. After three months' domiciliary chemotherapy the infil-

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PLATE XXIV

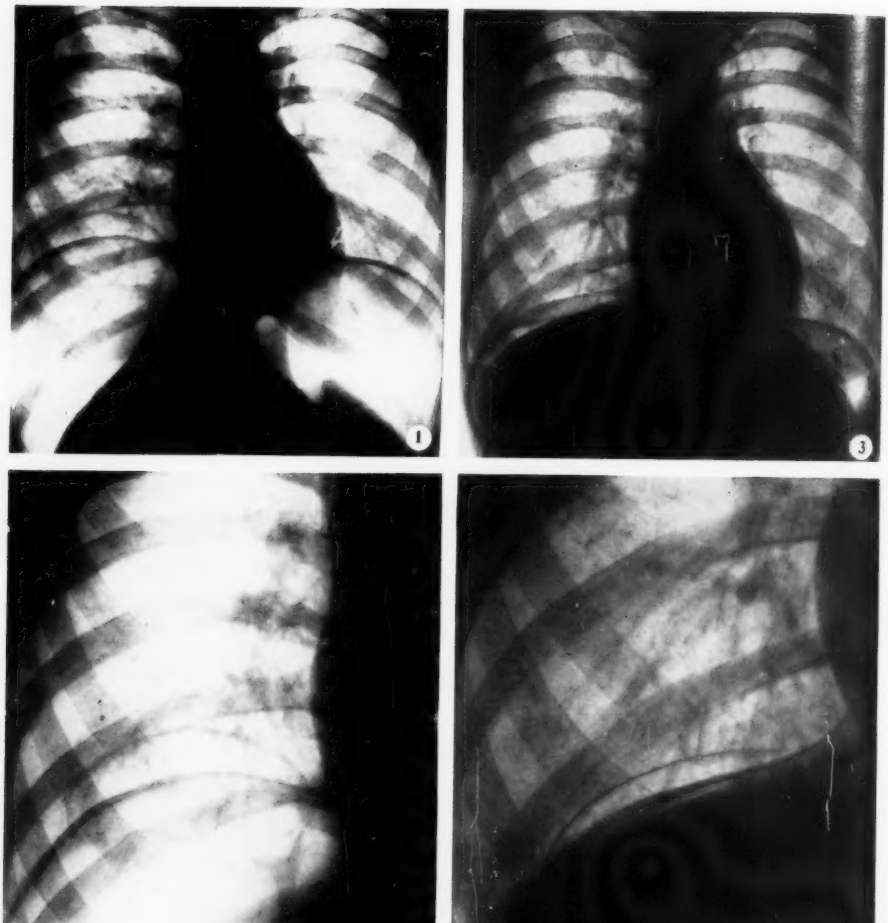

FIG. 1.—Pneumocele present at right base.

FIG. 2.—Close-up of pneumocele (P.A. view).

FIG. 3.—Pneumocele partially collapsed after air withdrawn.

FIG. 4.—Pneumoperitoneum has absorbed and liver returned to normal position. Pneumocele much smaller.

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trative lesions had regressed and the cavity was much smaller. A pneumoperitoneum was induced in July 1953 with closure of the cavity and further regression of the infiltration. Phrenic paralysis was not performed. Pneumoperitoneum treatment continued satisfactorily with refills of 1,000 c.c. weekly for three months and then fortnightly for six months. The intraperitoneal pressures during the last three months had not risen above +8 cm. of water. On routine chest radiograph a cyst-like structure (8·5 cm. by 4 cm.) was evident at the right base, apparently lying on the diaphragm (Figs. 1 and 2). Screening showed it to become larger on inspiration and this was confirmed with radiographs. Immediately following a refill of 1,000 c.c. with final pressures of +6 +7 cm. of water the pneumocele was seen to be larger in size. The refill needle was re-introduced about 2 inches above and to the left of the umbilicus, and with the needle tip tilted upwards into the subdiaphragmatic region 2,500 c.c. of air were withdrawn. The final pressure recorded was −8 −10 cm. of water. During this procedure the patient had no discomfort and afterwards, apart from feeling a " little flat," was quite well. Radiologically the pneumocele appeared to have largely collapsed (Fig. 3) and the pneumoperitoneum treatment was abandoned. Ten days later the liver had returned to its normal position and no air was visible under the diaphragm. A small bubble of air (Fig. 4), the remains of the pneumocele, could still be seen above the diaphragm, but in seventeen days' time this had also disappeared.

Discussion

This case is of interest in that the rare complication of diaphragmatic pneumocele occurred during pneumoperitoneum treatment. Most of the literature relating to this complication refers to the thoracoscopic observation of air-containing vesicles on the diaphragm when pneumothorax was present in addition to the pneumoperitoneum.

In this case the diaphragmatic pneumocele was noted nine months after the induction of the pneumoperitoneum, in the absence of any history of recent trauma or phrenic paralysis. During the three months prior to the development of this complication the intraperitoneal pressures had not risen above +8 cm. of water, which is not excessive. The patient had, however, been constipated during the previous six months and had strained a good deal at stool. This may have given rise to sharp increases of intraperitoneal pressure. The pneumocele was seen to become larger on inspiration and also immediately following a refill. After withdrawal of air from the peritoneum it was seen to be collapsed. This behaviour supports the presence of a small communication between the pneumocele and the peritoneal cavity.

Ross and Faber (1951) state that this condition may represent the herniation of peritoneum through a diaphragmatic defect, to lie under the diaphragmatic pleura, and is a potential precursor of a spontaneous pneumothorax. They correlate the size of the defect in the right diaphragm with the time when it may show itself. The smaller the defect the later in treatment is it likely to show itself, and then only when additional factors are present. The latter include excessive intraperitoneal pressure such as may result from straining at stool, persistent coughing or lifting heavy objects.

Johnson (1954) suggested that the liver moving upwards when the abdominal muscles are tensed could, by a piston-like action, produce excessive

intraperitoneal pressure under the right diaphragm. Indirect trauma may bring to light potential diaphragmatic defects, and so contribute to the formation of a pneumocele. The danger of diaphragmatic pneumocele lies in the possible development of a pneumothorax. The theory that air from the pneumoperitoneum causes the pneumothorax by tracking through the aortic or œsophageal hiatuses of the diaphragm into the mediastinum and then rupturing into the pleural space, as suggested by Banyai and Jurgens (1940), Simmonds (1946) and Loughead (1950), is not supported by available evidence. The present opinion is that the air passes directly through the diaphragm. It is probable that the condition of diaphragmatic pneumocele is the intermediate stage in some cases, particularly when pneumothorax complicates an established pneumoperitoneum. As a result of excessive intraperitoneal pressure produced by a combination of the factors mentioned above, together with some defect or weakness of the diaphragm, the pneumocele forms only to rupture into the pleural cavity with the formation of a pneumothorax. The apparent infrequency of its radiological observation may be related to the fact that the differential pressure between the intrapleural and intraperitoneal pressure is greatest some time after the pneumoperitoneum refill, and also the probable fleeting existence of the pneumocele before it ruptures. It would seem reasonable, if it is observed at any time, to withdraw immediately the air from the pneumoperitoneum and to terminate this treatment. When this complication occurs the patient should be put to bed and warned about making any unusual exertion or exposing himself to trauma of any kind, until the pneumoperitoneum has disappeared completely. Straining at stool while undergoing pneumoperitoneum treatment being a possible factor in producing a pneumocele, these patients should be advised to guard against constipation.

Summary

The complication of diaphragmatic pneumocele noted by radiography during pneumoperitoneum treatment is described, and the possible factors in its causation are mentioned.

It is considered that the occurrence of this complication is an indication for immediate withdrawal of air from the pneumoperitoneum and the termination of this treatment.

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LONG SURVIVAL IN UNTREATED LUNG CARCINOMA

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The natural history of lung carcinoma is a small facet of the problem of this disease and detailed information on long survival without treatment is accordingly limited. This paper reports the occurrence of lung carcinoma in five patients in whom the duration of the untreated disease, from the time of the first radiological abnormality, exceeded two years. Histological confirmation of the diagnosis was obtained in each case. All were squamous-cell carcinomata. Bronchial adenoma undergoing malignant change when a radiological abnormality may exist for many years (Evarts Graham, 1947; Umiker and Storey, 1952), and the so-called alveolar-cell carcinoma are excluded. The natural history of the alveolar-cell carcinoma may be protracted (Storey, Knudtson and Lawrence, 1953). Three other patients with slowly progressive lung shadows were seen during the same period and for various reasons thoracotomy was contra-indicated. The radiological shadow was present in each instance for over two years, a presumptive diagnosis of carcinoma of the lung was made, but, as histological confirmation was unobtainable, their case histories will not be described. These patients are alive and free from severe chest symptoms twenty-six months, twenty-eight months and thirty-three months from the time of the appearance of the radiological abnormality, two have developed rib erosion adjacent to the lesion, and no reasonable doubt exists in any of them as to the nature of the condition. These and the five case histories reported are from a total of 170 lung carcinomata diagnosed in the two-year period during which they were seen. The growths were all situated in the upper lobes of the lung and all the patients were males.

Many authoritative reports have referred to patients in whom the disease has run a long course without treatment, and it is widely accepted that this may happen. Sellors, Cruickshank and Billimoria (1947), reporting on 246 patients who underwent resection for lung carcinoma, state: "An important and common characteristic of these tumours is their insidious and silent growth. Several of our own cases could have been diagnosed by radiography a year before pneumonectomy—eighteen months in one case." Brock (1948) writes: "Occasionally one sees patients who have lived several years with the disease, particularly elderly patients with a slow-growing squamous-celled growth. These are the exceptions, and it must be remembered that the average expectation of life from the time the patient first consults his doctor is no more than six months." From a series of 1,000 patients, Mason (1949) describes one patient with a history of about five years, but points out that, whatever the treatment, most cases run a very much shorter course. Patients with histories

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of seven years and nine years are mentioned by Overholt and Schmidt (1949). Resection was carried out in both cases. The pathological type of growth was not described. Survival of a patient with untreated carcinoma of the lung for seven years was recorded by Moll (1949). Taylor and Waterhouse analysing 1,592 cases found, if 92 pneumonectomy cases were excluded, only three who lived three years or more, the maximum survival time being forty-three months. Out of 373 proven cases of squamous-cell carcinomata Carlisle, McDonald and Harrington (1951) found without resection only 3·6 per cent. surviving two years and no survivors for three years after the diagnosis had been made. On these figures, long survival without treatment must be accepted as being unusual.

Details of the five long survivors are given in the case reports. The diagnosis of carcinoma was in four cases verified by resection of the lung and in one by biopsy. The possibility of the neoplasm supervening on pre-existing disease during the period that the radiographic changes were present was, as far as possible, excluded by examination of the lung after operation in four of the five cases. Malignant change in simple lung scars has been amply considered by Raeburn and Spencer (1953). Drew (1953) finds no evidence that chronic lung disease predisposes to carcinoma. Carcinoma and chronic lung disease may be found in the lung as a fortuitous association of diseases without common etiology. It is sufficient to say that in the four lungs examined pathologically no evidence of benign tumour or other disease was found.

Case Reports

Case 1.—G.M., male aged 65, a foundry worker by trade. Smoked fifteen cigarettes a day for forty years. Patient's father and mother had died in old age of cerebral thrombosis. His brothers and sisters were well. During the winter of 1948 the patient had right-sided pleurisy which kept him in bed for three weeks. This recurred in the winter of 1949. In July 1950 a right inguinal herniorrhaphy was performed and three weeks later the pleuritic pain returned and he had several small hæmoptyses for the first time. A chest X-ray was taken (Fig. 1) which showed a right upper zone lesion as well as some infiltration in the lower zone which was thought to be due to a pulmonary embolus. The lesion in the upper lobe gradually increased in size over the next few months and exploration of the mass was advised. The patient did not accept this. He had a further chest X-ray in April 1952 (Fig. 2) and about this time started to have repeated staining of the sputum. On account of increasing pain in the chest, nocturnal cough and persistent brownish sputum he was readmitted to hospital. His X-ray in September 1953 is shown (Fig. 3). Bronchoscopy showed a normal bronchial tree. Malignant cells were not present in the sputum. No local or general contra-indication to exploration could be found and the patient was now anxious to be relieved of his symptoms. Right pneumonectomy was carried out in November 1953, forty-one months after the first radiological abnormality. At operation the pleura was lightly adherent to the fifth rib. The bulk of the tumour prevented any attempt to define the fissures. There were no palpable hilar glands or intrathoracic extensions of the growth. It seemed confined to the lung. The right lung was removed. The patient was discharged from hospital on the twenty-third day. There was a significant increase in dyspnœa, but his pain was relieved and he had no sputum.

FIG. 1 (Case 1).—First radiograph September 1950. Neoplasm visible in right upper zone. Other changes due to embolus.

FIG. 2 (Case 1).—Appearances in April 1952.

FIG. 3 (Case 1).—September 1953 at time of operation.

FIG. 4 (Case 2).—August 1947. Changes in left upper lobe after left-sided pneumonia.

FIG. 5 (Case 2).—May 1949. Increase in shadow. Presumptive diagnosis of carcinoma made.

FIG. 6 (Case 2).—Film at time of operation.

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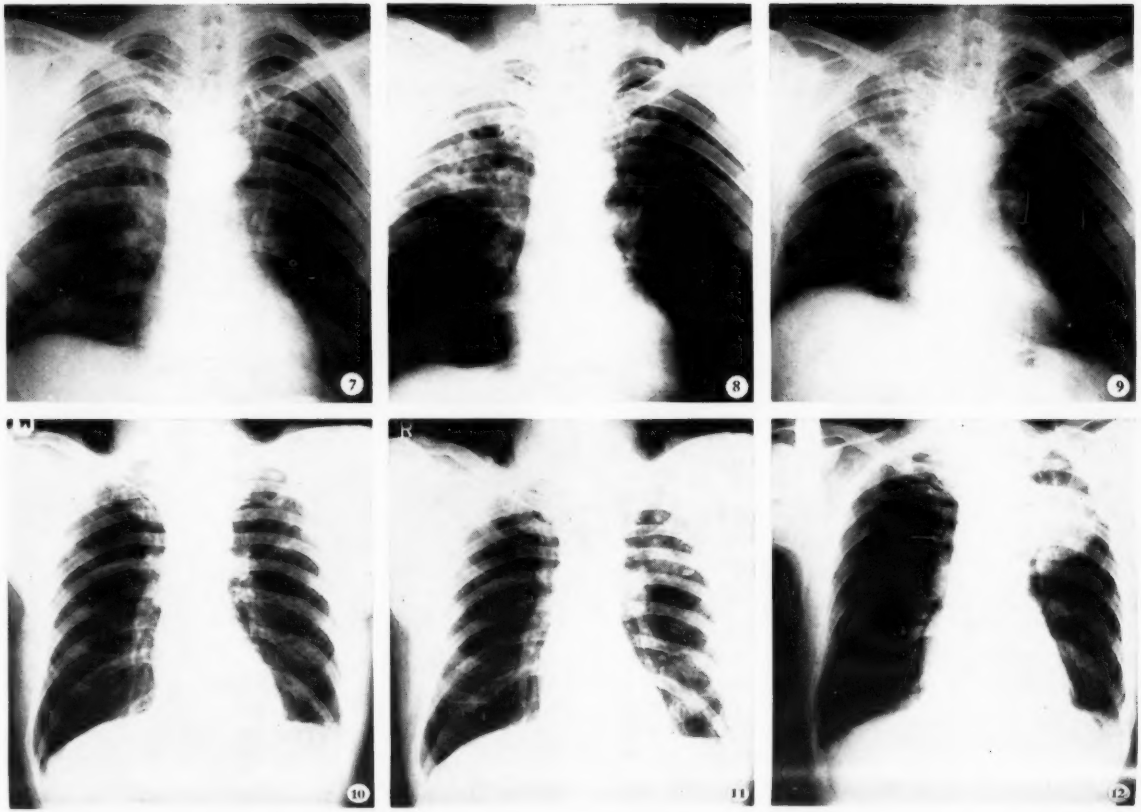

FIG. 7 (Case 3).—First radiograph November 1948. Right mid-zone infiltration with elevation of the fissure.

FIG. 8 (Case 3).—November 1952. Film following an increase in 1950.

FIG. 9 (Case 3).—July 1953. Increasing collapse of the right upper lobe. The lobe had been completely collapsed between this film and November 1952 (Fig. 9).

FIG. 10 (Case 5).—July 1950. Old tuberculous lesions both apices. Separate nodule visible over front end of third left rib.

FIG. 11 (Case 5).—Appreciable increase in size of lesion by September 1952.

FIG. 12 (Case 5).—December 1953 at time of admission to hospital. Diagnosis proved by left supraclavicular gland biopsy. No operation.

Pathology.—The specimen consisted of an excised lung. A portion of rib was attached to the upper lobe. Beneath this there were dense pleural condensations. Beneath these was a massive cavity 10·5 cm. in diameter. The interior of the cavity showed numerous fleshy papillary projections. There was infiltration of the wall.

Microscopically the lung was extensively infiltrated by a well-differentiated squamous-cell carcinoma. There were well-keratinised epithelial pearls. There was a tendency for the central cores of the cell masses to break down and become infected. The cavity was lined by infected squamous carcinoma.

There was extensive fibrosis of the lung substance in relation to the tumour.

The point of origin of the tumour in the lung tissue was not established.

Lymph nodes were not involved.

Case 2.—H.T., male aged 71, a retired locomotive driver. Smoked less than ten cigarettes daily for forty years. His father died aged 60 of carcinoma "of the liver." In 1946 the patient had left-sided pneumonia and he was in bed for six weeks. X-ray at that time showed a left upper zone opacity of lobar distribution. His symptoms subsided on chemotherapy and he resumed his usual activities. A residual left upper zone shadow remained in his X-ray during 1947 (Fig. 4). By May 1949 the shadow had increased (Fig. 5) and a presumptive diagnosis of carcinoma was made. In view of his age, absence of symptoms and doubt as to the diagnosis no operation was suggested. In April 1952 a further increase in the shadow was noted. He remained symptom free until December 1952, when he had his first hæmoptysis. He was first seen in January 1954, when he complained of loss of weight, cough and purulent blood-stained sputum. The patient said "he was unable to go on like this." His symptoms were severe. The sputum was repeatedly negative for A.F.B. and malignant cells. The hæmoglobin was 9·0 gm./100 c.c. Bronchoscopy showed the left upper lobe orifice to be irregular and narrowed, biopsy from it revealed normal bronchial mucosa. There was no bronchoscopic contra-indication to lobectomy. A course of 2 mega units of penicillin daily for ten days in hospital had no appreciable effect on his symptoms and he had become pyrexial. An X-ray in February 1954 is shown (Fig. 6). The lesion had extended and there was a suggestion of left lower lobe collapse. No contra-indication to operation could be found. Left upper lobectomy was performed in March 1954, eighty-nine months after the first radiological change. On opening the chest the left upper lobe was not seen. It had become one with the mediastinal structures and was approximately the shape and consistency of a kidney. It was totally airless and gave the impression of having been so for a long time. Mobilisation of the left upper lobe from the mediastinum necessitated division of the left phrenic nerve. The contralateral pleura was opened. The lesion seemed confined to the upper lobe. There was no means of confirming the diagnosis of neoplasm. Left upper lobectomy was carried out. His immediate convalescence was satisfactory, but he died from a pulmonary embolus on the twenty-third post-operative day. Necropsy confirmed this.

Pathology.—The specimen consisted of an excised lobe of lung. There were multiple pleural condensations. A mass of hypertrophic tissue blocked the main bronchus and this led into a cavity in which similar hypertrophic tissue formed the lining.

Microscopically there was a well-differentiated squamous-cell carcinoma. There were well-keratinised cell nests. Mitoses were frequent. The carcinoma appeared to have grown in the lung architecture and to have infiltrated in the

tissue spaces. There was a tendency for the central cores of the cell masses to break down and become infected.

There was well-marked fibrosis of the surrounding lung substance.

None of the lymph nodes examined showed evidence of invasion.

CASE 3.—S.Z., male aged 51. A farm worker since the age of 12. Smoked ten cigarettes a day for the last twenty years. No relevant family or previous history. First complained of cough and lassitude in November 1948. Chest X-ray (Fig. 7) at that time showed right mid-zone infiltration. The sputum was persistently negative for tubercle bacilli and this patient was kept under out-patient observation and remained at work. In 1950 the shadow in his X-ray film increased, he was given penicillin and the appearances improved. Moist sounds at the right apex remained. A diagnosis of pulmonary tuberculosis was made and the patient was admitted to a sanatorium. By 1952 the right upper zone shadow had again increased (Fig. 8) and by March of 1953 the right upper lobe had become atelectatic. Penicillin and a six weeks' course of streptomycin produced some reaeration of the right upper lobe (Fig. 9). The patient was seen in September 1953. Bronchoscopy revealed the right upper lobe orifice to be completely stenosed. There was no ulceration of the mucosa. Biopsy from the stenosed area showed no evidence of carcinoma of the bronchus. The patient was admitted for thoracotomy. There had been no hæmoptysis throughout the course of his illness. His only complaint was of right-sided chest pain. The sputum was under 1 oz. daily in amount and had never been direct smear or culture positive for tubercle bacilli. There were no local or general signs of inoperability. In October 1953, fifty-eight months after the original X-ray abnormality, the right lung was removed. At operation a hard mass about the size of a golf ball was palpable around the right upper lobe bronchus. The lung was freed intra-pleurally without difficulty. Glands could be felt at the hilum of the lung. An attempt to conserve the middle and lower lobes was unsuccessful. Right pneumonectomy was carried out. The patient was discharged from hospital on the twentieth post-operative day. He is free from signs of recurrence six months after operation.

Pathology.—The specimen consisted of an excised right lung. There were pleural adhesions and condensations on the lateral surface. The upper portion contained a mass some 4 cm. in greatest measurement. There was bronchiectasis distal to this.

Microscopically the lesion was a grossly infected squamous-cell carcinoma. The carcinoma was reasonably well differentiated. There were cell nests present which showed a degree of keratinisation. There had been considerable infection and necrosis both of tumour and of the central cores. There was fibrosis of the lung substance.

CASE 4.—T.D., male aged 64. Had worked as a miner for forty years and smoked about seven cigarettes a day since adolescence. The patient's brother had died of lung carcinoma at the age of 59 and his father of carcinoma of the rectum when 72. The only relevant previous history was of severe right-sided chest pain of abrupt onset associated with hæmoptysis whilst at work in 1947. The patient was off work for three months. His chest X-ray at that time was normal. He remained well till late 1951, when he noticed increase in his cough. X-ray of his chest in January 1952 showed right upper zone infiltration. He was put off work. By April 1952 the lesion had increased and the patient was admitted to hospital. The sputum was negative for tubercle bacilli and malignant cells on repeated examination. Bronchoscopy (April 1952) showed the

right upper lobe orifice to be evenly contracted as compared to the left upper lobe orifice. The lumen was patent, however, and the segmental bronchi were visible. There was no increased rigidity or ulceration and a biopsy from the right upper lobe orifice showed normal mucosa. A bronchogram was not performed. A diagnosis of suppurative pneumonitis was made and the patient given 2 mega units of penicillin daily for two weeks. The X-ray shadow resolved under this treatment and the patient returned to work. He attended regularly until November 1952, when some increase in the infiltration was noted. For the next fourteen months he remained symptom free at full work and did not attend again until January 1954. He then complained of severe pain in the right chest and pains in both legs of a neuritic nature. His X-ray showed complete right upper lobe atelectasis. The patient was readmitted. There had been no hæmoptysis or other symptoms from the beginning of the illness until three weeks before admission, when the chest and leg pains started, apart from loss of 14 lb. weight over the previous two years. No local or general signs of inoperability existed. At bronchoscopy the carina was normal, but a satisfactory view of the right upper lobe orifice could not be obtained on indirect vision. It appeared completely blocked through the telescope. A blind biopsy of the right upper lobe orifice produced normal mucosa. The right lung was removed twenty-five months after the first radiological abnormality. At operation the pleura over the lung was thickened and opaque, the lobe had an indiarubber feel. There was glandular involvement of the hilum. There was no macroscopic dissemination of the growth elsewhere in the hemi-thorax. The patient was relieved of his pain and discharged on the sixteenth post-operative day.

Pathology.—The specimen consisted of an excised right lung. The main lower lobe bronchus was blocked and the blockage extended for a centimetre along its length. This was subtended by a firm tumorous mass some 4 cm. in greatest measurement. The lung distal to this was extensively infiltrated and cavitated.

Microscopically the lesion was a well-differentiated squamous-cell carcinoma with well-keratinised cell nests. It infiltrated the lung in plaques and trabeculæ. There was considerable secondary infection of the central cores.

Case 5.—R.L., male aged 56, the proprietor of a small general stores. Smoked less than ten cigarettes a day for thirty years. No relevant previous history. In July 1950 the patient was X-rayed because of a sinus over the sternum; a diagnosis of bilateral fibroid pthisis was made. At that time a discrete opacity was visible in the X-ray on the same level as the front end of the third left rib (Fig. 10). By January 1952 the lesion had increased in size and in spite of chemotherapy further increases were noted in September 1952 (Fig. 11) and April 1953. The patient had no pain, no hæmoptysis and less than 1 oz. of sputum daily since May 1952. The sputum had on occasion been positive for A.F.B., but no malignant cells were isolated. He was first seen toward the end of 1953. Bronchoscopy showed no abnormality. A biopsy from the left upper lobe orifice was normal. In December 1953 he was admitted to hospital for thoracotomy forty months after the first radiological change (Fig. 12). During the preceding month, however, a gland had appeared in the left supraclavicular region. The gland was excised and found to be invaded. The patient was discharged in March 1954, forty-four months after the first X-ray change. He was still free from distressing chest symptoms, but had some weakness of the left arm. Thoracotomy was not undertaken.

Pathology.—The specimen was that of an excised mass of glands. The individual glands were discrete. They felt firm. To the naked eye they appeared white and infiltrated.

Microscopically the glands were infiltrated by a well-differentiated squamous-cell carcinoma. Keratin formation and cell nest formation were frequent. There was a tendency for the centre of the masses these glands formed to break down and become infected.

Discussion

A study of patients with exceptionally long histories of the disease leads naturally to a consideration of its average length of history. Little is known of this aspect of the disease. The actual time of origin of the lesion in the lung cannot possibly be determined other than by a guess. For this reason observers have assessed and recorded the average span of the disease in a variety of ways. The time from first symptoms to death, presumptive diagnosis to death, first visit to doctor to death, and first radiological change to death, have been the methods used. Taylor and Waterhouse (1950) recorded 4·4 months as the mean survival from time of diagnosis and 5·5 months as the average duration of symptoms before diagnosis. Thus, the average duration of the disease from its onset untreated, to death, is 9·9 months, when the onset of the symptoms corresponds to the onset of the disease. As the authors of the paper point out, this is not to be assumed. Another average figure of significance would seem to be the average duration of the disease from the time of the first radiological abnormality to death, for the particular cell type of carcinoma concerned. This figure is objective, as applicable to whole series as to the individual, and emphasises the only means whereby a presumptive diagnosis can be reached in the great majority of cases. It is not free from anomaly, however. The diagnosis may be made at bronchoscopy or by examination of the sputum for cells in a patient with a normal chest radiograph; the first radiological evidence of the disease may be metastatic hilar glands from an invisible lung primary, and modern chemotherapy may produce complete resolution of a radiological shadow due to malignant obstruction of a bronchus (Simon, 1953). It is probable that this average figure, namely the time from first radiological abnormality to death, would be considerably longer, especially for squamous-cell growths, than the figure of 4·4 months from diagnosis to death. The acceptance of a longer average duration of the disease is a stimulus to even earlier diagnosis and exploration of any doubtful shadow occurring in the chest film of a patient in the cancer age group. When for some reason delay in diagnosis has occurred, the clinician may hope, if the patient is symptom free and the lesion resolving radiologically, that the condition is not neoplastic. The risks to which the patient is being exposed by such a line of thought are more apparent, the more aware the clinician is of the long course the disease may take, and the great variability in the progress of radiological shadows. In addition, the complete resolution of a radiological shadow under chemotherapy must be regarded as a wholly inconclusive diagnostic criterion, even when the picture remains clear for many months.

A reason for the apparent high incidence of long survival (five proven and three presumptive carcinomata from a total of 170 cases), compared with

previous figures, must be put forward. The explanation is twofold. The more widespread use of chest radiography will naturally detect greater numbers than formerly with early radiological evidence of the disease, and, if the yardstick of long survival is taken as the time from the first radiological change to death, a potentially larger number will be found with this early evidence. Had the time from final diagnosis been used, only one case (Case 5) could be considered as a long survivor without treatment, for in four cases the confirmed diagnosis was reached only after thoracotomy and in three the diagnosis remains presumptive. This accounts for the high incidence, but the case histories offer no explanation for the slow growth of the tumours. They do confirm, however, what is well known—that the highly differentiated squamous-cell carcinoma is likely to grow slowly, that confirmation of the diagnosis in upper lobe growths may be difficult by bronchoscopic biopsy, and that the length of time the lesion has been present has in itself no influence on its resectability. It is of interest that in two of the five cases spread to the hilar glands had not occurred. Such cases as these clearly offer the best prognosis after surgery, and account must be taken of them in assessing survival after operation for periods less than five years.

Summary

1. The case histories of five patients with carcinoma of the lung who survived for long periods from the time of the initial radiological change without treatment are described.

2. Reasons for the apparent high incidence of long survival in this small series are discussed.

I am greatly indebted to Dr. A. P. Prior for his observations on the pathology of these tumours.

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LIMITATIONS OF THE POSTERO-ANTERIOR CHEST FILM

By R. L. Sadler

From the Chest Clinic, Doncaster

Increasing use is made of miniature films at Miniature Mass Radiography units and chest clinics, as a time-saving examination of patients referred by general practitioners. Such patients often have symptoms suggesting chest disease, and among them a higher proportion of " positive findings " arises than in most groups examined by mass radiography surveys. It should always be kept in mind that the postero-anterior chest film may appear normal in a patient who has well-marked pulmonary disease.

Some pathological conditions of the chest may produce no radiological change—*e.g.*, early miliary tuberculosis, pulmonary embolus from which there is no infarct, inflammatory diseases or neoplasms of the bronchi where no secondary lung changes have arisen (Rabin, 1952).

Other diseases may give rise to X-ray opacities not seen in the P.A. film but which are visible when other views of the chest are taken. For example, an opacity may be overlapped by a more radio-opaque structure, or its thickest dimension may not lie parallel to the X-ray beam in a straight film. Fairly dense pulmonary shadows can be concealed behind the heart and mediastinal vessels or bones of the thorax; softer opacities in the lung apices may be lost in the shadows cast by the sternomastoids. Indeed Kerley (1943) notes that 20 per cent. of the lung tissue is not visible in the P.A. film.

An example familiar to chest workers, of pathological shadows overlapped in the P.A. film, is seen in the case of enlarged bronchial lymph glands. Sometimes the glandular component of a primary tuberculous complex is wholly or partly covered by the mediastinal structures, and it is then difficult to be certain whether adenopathy or whether prominent vascular shadows are the causative factors (Grzybowski, 1954). Lateral X-rays and tomograms are commonly used to show up obscured bronchial gland enlargement. Figs. 1 and 2 illustrate how even grossly enlarged and calcified hilar glands may be invisible behind the great vessels in the P.A. projection.

Post-primary tuberculous lesions may be similarly obscured. Trail and Kerley (1943) illustrate how early tuberculous foci may be concealed in the P.A. film behind the vascular shadow in the right upper lobe or by overlapping bony shadows.

Crofton (1949), writing on basal tuberculosis, states that such lesions are reported more frequently in the right side of the chest but expresses the view that lesions in the left have often been missed because they are hidden behind the heart in the usual P.A. radiograph. It is common experience that " round shadows," of tubercular or non-tubercular origin, when lying directly behind the heart, are apt to be completely concealed in this projection.

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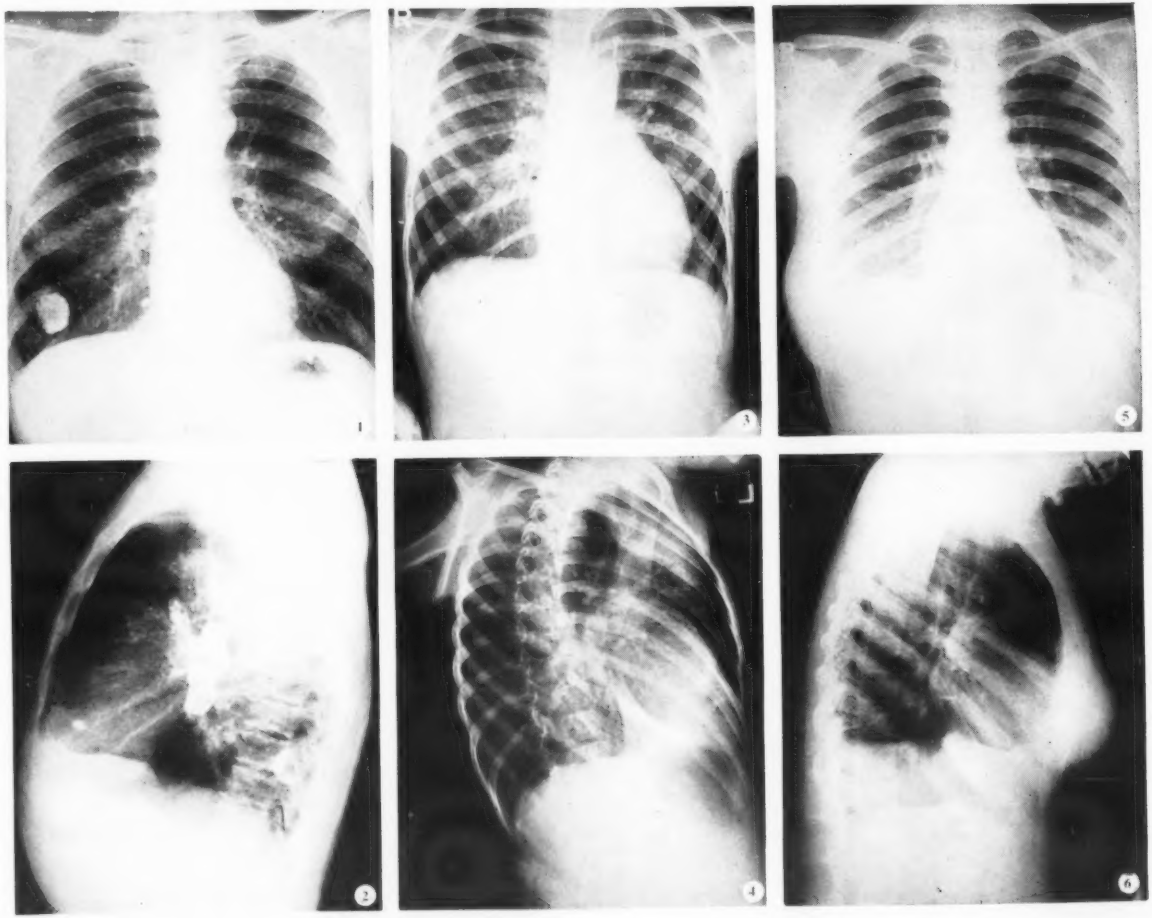

FIG. 1.—P.A. film showing calcified tuberculous focus in lung parenchyma.

FIG. 2.—Lateral film of same case shows a row of calcified bronchial glands invisible in the P.A. view.

FIG. 3.—P.A. film of girl aged 7. Slight hyper-translucency at left base.

FIG. 4. — Posterior-oblique view shows atelectatic segment.

FIG. 5.—Apparently normal film of young woman with physical signs of right basal pleural effusion.

FIG. 6.—Lateral film of same case demonstrates the effusion.

To face p. 318

An atelectatic left lower lobe is often overlapped by the heart shadow, but this is not usually missed in the P.A. film. Even if there is insufficient penetration to show the straight edge of the collapsed lobe through the cardiac shadow compensatory emphysema in the uncollapsed part of the lung will give the clue. If however the atelectasis involves only a segment this may not be obvious. In Fig. 3 a collapsed posterior basic segment might well have been undiagnosed if the P.A. film alone had been read. It was not detected on the lateral radiograph either, and a carefully positioned posterior-oblique view was required to bring the maximum density of the collapsed segment into line with the X-ray beam (Fig. 4).

Pleural effusion is frequently encountered and its presence may sometimes be detected by physical examination at a stage when it is insufficient in quantity to produce an opacity in the P.A. film. Rigler (1949) considers that at least 300 c.c. of pleural fluid must be present before it is visible with the patient in the usual upright position and he advocates radiographs in a lateral decubitus to demonstrate small effusions. When an appreciable effusion is not visible in the straight X-ray this is usually because it is localised—for example, it may lie in and above the anterior fossa of the diaphragm. In the P.A. view only a small depth of fluid, but in the lateral view the maximum thickness of it, is then presented to the X-ray beam. In Figs. 5 and 6 the distribution of the fluid at the base of the right chest accounts for an appearance of a moderate effusion in the lateral film with a clear P.A. picture.

Summary

Several examples demonstrating the limited diagnostic value of the postero-anterior film are illustrated, assuming it is used as the sole measure of examination. Surveys or individual examinations by miniature P.A. photographs may fail to diagnose a proportion of cases having chest disease. The value of lateral and oblique films and tomographs in selected cases is emphasised.

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REVIEWS OF BOOKS

Recent Advances in Chemotherapy—Vol. III, *Antibiotics*. By F. C. O. VALENTINE and R. A. SHOOTER. London: J. and A. Churchill Ltd. 1954. Pp. viii + 292. 7 illus. 27s. 6d.

Dr. G. M. Findlay did not live to complete the third volume of the third edition of *Recent Advances in Chemotherapy*. The task has been taken on by Drs. Valentine and Shooter, whose aim has been to outline the fundamental principles of the use of antibiotics and at the same time to give a survey of modern methods of treatment.

The first five chapters deal with the antibiotics in common use; then follow short chapters on resistance and on general principles. The remaining chapters (VIII to XIX) deal with the various types of infection due to bacteria, and the twentieth (and last) chapter with the rickettsiæ and viruses.

The authors have certainly succeeded in their aim of giving an up-to-date and reliable account of their subject. The facts are clearly presented and the literature is well and thoroughly reviewed. Chapters on tuberculosis (chapters II and XII) give a balanced account of the striking advances made in this field in the last few years.

A few minor criticisms may be made. Since Volumes I and II dealt with groups of diseases, it is a little illogical to give the third volume the title "Antibiotics." For one thing it includes the sulphonamides, para-amino-salicylic acid and isoniazid, which are not antibiotics; a better title would surely have been "Infections caused by bacteria, rickettsiæ and viruses." A number of misprints were noticed—for example, p. 144 "endotheliazation," p. 166 "tractible," p. 228 "benefitted," p. 280 "gastrio-intestinal." It is to be hoped that in a further edition the authors will remedy these minor blemishes in what is, in other ways, a clearly and interestingly written account of this branch of chemotherapy.

ROBERT KNOX.

Pneumoconiosis Abstracts, Volume II. Reprinted from the *Bulletin of Hygiene* for the Years 1939 to 1950 inclusive. London: Sir Isaac Pitman and Sons Ltd. 1954. Pp. 518. 80s.

In the April 1954 number of the Journal the first volume of Pneumoconiosis Abstracts (1926-1938) was reviewed. The second volume, which has now been published, covers the period 1939-1950 inclusive. Though this period is a year shorter than that covered by the first volume, the second volume contains 171 more pages than the first, and abstracts of many more articles. It reflects the increasing interest taken, during a decade which included the war years, in the pneumoconioses, and also the intensive investigations which were made into the effects of dusts and fumes other than silica and asbestos. The section on "pneumoconiosis caused by other inorganic dusts" takes up 81 pages in the second volume, whereas in the first, only 22 pages were devoted to this section. Here will be found abstracts on many metallic dusts such as aluminium, antimony, beryllium, cadmium, cobalt, iron and copper; on basic slag, boiler scale and cement; on glass, graphite and fuller's earth. The recent voluminous work on beryllium is grouped for handy reference, and the many articles on

researches into the effects of radio-opaque dusts—which have altered unobtrusively the approach to the interpretation of X-ray chest films in general—have been set out in convenient juxtaposition.

Professor E. L. Collis has again contributed the greatest number of abstracts (over 200) and he is followed closely by the late Dr. S. Roodhouse Gloyne, Dr. E. L. Middleton and Dr. Thomas Bedford, in that order. These four distinguished authorities together are responsible for more than half of the thousand-plus abstracts which the book contains.

Dr. E. L. Middleton has again edited the second volume and prepared the index with characteristic care and integrity; and it was fortunate that he was able to devote his time and wide experience to such a stupendous and worthwhile task. No one could have done it better, nor indeed as well, and students of the pneumoconioses will always be indebted to him. He, with the staff of the *Bulletin of Hygiene*, and the publishers and printers are to be congratulated on the general excellence and elegance of the two volumes. It would be ungrateful on the part of the reviewer to suggest again that the price is too high. But the price will probably limit the circulation, and that will be a great pity.

A. I. G. McLAUGHLIN.

Guide to the Classification and Identification of the Actinomycetes and their Antibiotics. By SELMAN A. WAKSMAN and HUBERT A. LECHAVALIER. Published by the Williams and Wilkins Company, Baltimore (London: Baillière, Tindall and Cox). 1953. Pp. 236. Price 38s. 6d.

Prior to 1944 the interest aroused in the minds of clinicians and most laboratory workers by the word "Actinomycetes" was limited to its significance in connection with actinomycosis and possibly an occasional case of nocardiosis. With the discovery of streptomycin, and the beginning of intensive systematic studies of the antibiotic-producing properties of fungi, the actinomycetes took on a new significance. Here indeed was a happy hunting ground in the search for new antibiotics, and such drugs as chloramphenicol, chlortetracycline (aureomycin) and oxytetracycline (terramycin) were discovered in the course of studies of this group.

The problems confronting the mycologist in the classification of fungi are legion, and they were not simplified by the sudden increase in the number of new strains described in connection with antibiotics. Many of these were not recognised, owing to the limitations of systems of classification, as strains that had previously been described, and new names were accordingly given to them. Out of the resulting chaos Dr. Waksman and Dr. Lechavalier have made most commendable sense. Their book is intended primarily to facilitate the identification of the actinomycetes, of which 200 species are described, and of the antibiotics they produce. Summaries of the methods of production and extraction, physical and chemical properties, biological activity and toxicity are given for over 100 of these, and relevant references are provided in each case to reports from which detailed information may be obtained.

This guide will be of immense value to the laboratory worker confronted with an antibiotic-producing fungus not previously known to him and requiring identification and further study. To the clinician, however, its value will be extremely limited, since detailed information about specific antibacterial activity, dosage systems and toxic effects is not given.

J. ROBERT MAY.

British Medical Bulletin. Vol. X, No. 2: Tuberculosis. London: The British Council. 1954. Pp. 159. 15s.

The second number of the *British Medical Bulletin* (Vol. X) for 1954 is devoted to the subject of tuberculosis and contains an account by experts, in their particular sphere, of current therapeutic procedures as well as of recent achievements in prevention and research. The decline of tuberculosis mortality and its relation to the introduction of general public health measures of prevention, chemotherapy and collapse therapy and surgery are all discussed. On the other hand, the notification rate of new cases over the past decade is in striking and unfavourable contrast to the decline in mortality rate and gives no cause for complacency. It has, in fact, come to be recognised that a decline in the number of new cases gives the correct indication of the effectiveness of preventive measures.

The development of the Chest Clinic since the inception of the National Health Service is discussed and other subjects surveyed include the problem of tuberculosis in industry; the epidemiology of tuberculosis, its prevention by vaccination; and the respective merits of B.C.G. and the vole bacillus. Some problems in primary tuberculosis are also considered. The evolution of controlled trials by the Medical Research Council's Tuberculosis Research Unit is described and the important problem of drug resistance arising from the introduction of these drugs is discussed. There follows a well-balanced contribution on the clinical use of antibacterial drugs in pulmonary tuberculosis. The place of collapse therapy, especially that of artificial pneumothorax, is also surveyed, together with the varied surgical measures now established.

This volume will stimulate every reader even if he does not necessarily agree with all the viewpoints expressed, and it is particularly commendable that a balance should have been so well struck between research, prevention and treatment. It will indeed make a wide appeal for, as Dr. D'Arcy Hart observes in his introduction, " there is no branch of medicine attracting greater activity at the present time."

PHILIP ELLMAN.

Brompton Hospital Reports. Vol. XXII. London: Research Department of the Hospital. 1953. Pp. x+175. Illus. 15s.

Volume XXII of these reports, edited by Drs. Maurice Davidson and Foster-Carter, is the last volume confined purely to the Brompton Hospital. Future issues will represent also the work of the London Chest Hospital and the Institute of Diseases of the Chest. To this end an Editorial Board representing all these institutions has been formed.

The contributions in this volume have, as usual, all appeared previously in various medical journals and cover such important topics as the present status of lung resection for pulmonary tuberculosis by F. H. Young, carcinoma of the lung by Sir Clement Price Thomas, broncho-pulmonary aspergillosis by K. F. W. Hinson, A. J. Moon and N. S. Plummer, chronic lung disease with diffuse nodules in reticular radiographic shadows by J. G. Scadding, intrathoracic and intra-bronchial lipomata by J. Smart, valvotomy in pregnancy by Sir R. C. Brock and lymphangitis carcinomatosa by J. T. Harold.

The usual high standard of this production has been maintained.

PHILIP ELLMAN.

X-Ray Diagnosis of Chest Diseases. By COLEMAN B. RABIN. London: Baillière, Tindall and Cox. 1954. Pp. xi+208. 288 Illus. Price 91s. 6d. First Edition.

Dr. Rabin is primarily a chest physician, and only secondarily a radiologist. It is surprising, therefore, to find that in this book his approach has been entirely radiological; that is to say, he concerns himself with radiographic appearances and endeavours to relate these to underlying pathological processes. This way of presenting the subject allows the author to concentrate in the first place on principles of radiological interpretation as they apply in the chest, rather than to discuss disease entities with a description of their radiographic characteristics.

Most text-books of radiology adopt the latter approach, and this gives the present volume a special merit. The prime duty of the radiologist is to think in terms of shadows and their significance, as representing masses of healthy or diseased tissue in a three-dimensional space. He must always have before him this sense of spacial relationship for, as Brock teaches, the localisation of a lesion is a major part of diagnosis.

The first section of this book deals with general considerations in which the influence of the position of tube and patient are discussed, pitfalls pointed out, the anatomy of pleura and lung described, and the art of fluoroscopy set out in some detail. This is a most valuable section for the student of radiology.

There follows a section on " general roentgen pathology." Here the author discusses the manifestations of single pathological processes, without necessarily relating them to a disease syndrome. To the value of this section, allusion has already been made. Regional pathology and disease entities are treated in a further section, and the volume concludes with a short section in which the author discusses the differential diagnosis of certain specific types of shadowing, *e.g.*, linear, round circumscribed opacities, cavities.

From the clinical point of view, the book may be open to criticism for certain dogmatisms, which are perhaps inevitable in a book which cannot within its compass adequately cover the clinical aspects.

The general format is excellent, but the numerous illustrations suffer from a slight graininess which mars them æsthetically, although they seldom fail adequately to show the condition described.

A minor criticism of style concerns the use of the word " visualised " when the author means " seen." This usage is becoming very common but is incorrect. The word " visualised " has always meant to the reviewer " to see with the mind, and not with the eye."

This is a first-rate book for the student setting out on a career of diagnostic radiology, or for the chest physician who wishes to complement his clinical approach by radiological study.

A. M. RACKOW.

La Pratique du Pneumothorax Thérapeutique. By J. DUMAREST, P. GALY, J. GERMAIN, in collaboration with F. PARODI. Paris: Masson et Cie. 1954 (6th edition). Pp. 386, 18 illus. 1,500 frs.

The authors of this work, on the treatment of pulmonary tuberculosis with artificial pneumothorax, are all enthusiasts for this form of therapy, and descend directly from the Forlanini school via the late Frederic Dumarest, who was co-author of the five preceding editions. The previous edition was

published just before the antibiotic era (1945) and the present one has been considerably revised.

In eleven well-ordered chapters all aspects of artificial pneumothorax treatment are discussed. A discussion is included on the mode of action of pneumothorax and there is an interesting summary of the history of the method. Extrapleural pneumothorax, pneumoperitoneum and postural retention are briefly discussed.

Despite their enthusiasm for artificial pneumothorax the authors stress that, in using a localised technique to deal with a local aspect of the disease, one must never lose sight of the general nature of the disease. Pneumothorax is only part of the treatment and is indicated in selected cases. The method is advocated in conjunction with other methods of treatment, and chemotherapy combined with antibiotics is suggested to facilitate the early induction of pneumothorax in acute exudative conditions.

The thorny question of the treatment of the small circumscribed post-primary lesion in the young adult is discussed, where tubercle bacilli are not found, symptoms are absent, and tomography does not show cavitation. The respective merits of antibiotics, watchful expectancy, and collapse therapy are discussed. Surprisingly the authors are in favour, in general, of pneumoperitoneum (with bed rest). They do not even mention the Transatlantic tendency to resect such lesions.

Again, most readers in this country will be surprised to see that the authors use nitrogen for induction and refills. The reason given, that nitrogen is more slowly absorbed than other gases, does not seem adequate when it is recalled that air contains 80 per cent. nitrogen. Indeed the figures given by the authors for volumes of gas used and frequency of refills do not seem significantly different from those pertaining to the use of air.

Surprising omissions from what is, on the whole a well-balanced presentation are: reference to the importance of the same doctor—wherever possible—attending the patient throughout treatment; the importance of sharp needles; reference to the literature in general and English literature in particular; the prognostic significance of multilobular cavitation.

At this stage in the evolution of the treatment of pulmonary tuberculosis, when in many schools combined chemotherapy and antibiotics and surgical resection are so frequently advocated and artificial pneumothorax so frequently deprecated, one looks to an authoritative work on artificial pneumothorax for a clear statement of the relation of such treatment to others at the present time. Absence of any detailed numerical and statistical statement of the authors' results precludes any comparison with other workers' results.

To those who have never practised the method but wish to learn, the book presents detailed information in an assimilable form. To those who practise the method haphazardly it presents an excellent corrective. To those skilled in the method it is full of interest. To those who wish to know whether artificial pneumothorax should be more freely advocated or more often condemned it offers stimulating views but no conclusive evidence.

AUBREY KAGAN.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

The Anatomy of the Bronchial Tree, with special reference to the surgery of lung abscess. By R. C. Brock. London: Oxford University Press. 1954. Pp. 250. 286 Illus. Price 45s.

A Practical Manual of Diseases of the Chest. By Maurice Davidson. London: Oxford University Press. 1954. Pp. 658. 261 Illus. Price 84s. Fourth Edition.

The Surgery of Pulmonary Tuberculosis. By James H. Forsee. London: Henry Kimpton. 1954. Pp. 208. 59 Illus. Price 48s.

Anatomy of the Bronchovascular System, its application to surgery. By George L. Birnbaum. Chicago: The Year Book Publishers. 1954. (Distributed in Great Britain by Interscience Publishers Ltd.) Pp. xv+299. Illus. Price 112s.

Tuberculoma of the Lung. By Olle Hillerdal. Copenhagen: Ejnar Munksgaard. 1954. Pp. 190. Illus. Price 45s.

BCG and Vole Vaccination. A Practical Handbook. By K. Neville Irvine. London: N.A.P.T. 1954. Pp. 96. 10 illus. 12s. 6d.

Tuberculosis Index and Abstracts of Current Literature Quarterly. June 1954. Vol. 9, No. 2. London: N.A.P.T. Price 25s., per year $5.

Health Horizon. Quarterly. Summer 1954. London: N.A.P.T. 2s. 6d., per year 10s

Practical Electrocardiography. By Henry J. L. Marriott. London: Baillière, Tindall and Cox. 1954. Pp. xii+172. 115 illus. 38s. 6d.

Transactions of the 13th Conference on the Chemotherapy of Tuberculosis. St. Louis: Veterans Administration Area Medical Office. 1954. Pp. vi+442. (No price indicated.)

Die BCG-Schutzimpfung. By R. Griesbach. Stuttgart: Georg Thieme Verlag. 1954. Pp. xii+330. D.M. 16.50.

REPORTS

MEDICAL RESEARCH COUNCIL

Committee for Research on Social and Environmental Health: Sub-Committee on Mass Miniature Radiography

"The Sub-Committee feel that the prospects of controlling tuberculosis are at present so favourable that more intensive efforts are required on the part of MMR units. Investigation of other abnormalities should be deferred until the tuberculosis hazard is more completely eradicated."

The following is a summary of a report of the Sub-Committee:

1. In view of the present falling death rate from and the maintained high incidence rate of pulmonary tuberculosis, it is strongly recommended that an intensive effort be made to mobilise facilities and so hasten the eradication of the disease from the population.

2. It is concluded that, unless there are special considerations, re-examination of the same population (*i.e.*, the same individuals) by MMR at intervals of less than three years for the sole object of finding cases of pulmonary tuberculosis is not justifiable for medical or economic reasons.

3. It is recommended that MMR units should only screen population groups to select abnormal cases and refer them for further examination and not attempt to be fully diagnostic.

4. It is considered that it is not worth while to examine for pulmonary tuberculosis alone, by this technique, school children. Persons over the age of 35 also merit separate consideration with regard to repeat examination, because of the low yield of significant findings on re-examination.

5. It is thought that the two best methods of using MMR are: (i) examination of symptomatic cases referred by doctors, and (ii) the grouping of units for comprehensive surveys of "black spots."

6. Attention is drawn to the need for standardised terminology of the findings by MMR and a classification has been proposed for pulmonary tuberculosis discovered in this way.

7. The relative merits of static and mobile units have been considered and the points to be taken into account in making arrangements for units in an area have been detailed.

Copies of this report can be obtained from the Ministry of Health (M.R.C. 531687. S.E.H. 53122. M.M.R. 5317).

BRITISH LEGION VILLAGE (1925-1954)

We have received a souvenir brochure which is beautifully illustrated and concentrates particularly on the problem of rehabilitation and the training received in a series of occupations. A general summary is given of the great achievements that have been carried through in the British Legion Village since it began its work in 1925, offering as it does a worth-while future to ex-service men and women suffering from tuberculosis.

TUBERCULOSIS CONTROL IN MANITOBA

We give below some significant observations from the Report of the Medical Director of the Sanatorium Board of Manitoba for 1953:

"The most remarkable development regarding tuberculosis during recent years has been in treatment. Streptomycin, which was the first drug to have a specific action against the tubercle bacillus, opened a new era. With the discovery of one drug others soon followed and excisional surgical techniques were made possible that could not be envisaged heretofore. All patients initially are treated with two or more of these antimicrobial drugs for several months. After maximum clearing, if a significant residual focus remains it is resected. Collapse therapy by pneumothorax has been abandoned although thoracoplasty operations are done for certain cases when resection is contraindicated. All resected specimens are examined pathologically and correlated with clinical, radiological and bacteriological studies. At present we are riding the crest of resection surgery and it may be that after more prolonged observation of long-term chemotherapy less surgery will be considered necessary. The dramatic effects of drugs and surgery should not dim our appreciation of the established principles of the cure—rest, teaching and sanatorium régime. Most new cases on drug treatment become sputum negative in a few months and sanatorium superintendents are finding it more difficult to keep patients in sanatorium long enough. Although an increasing number of discharged patients are receiving drugs as out-patients, this practice is discouraged and dependent upon sanatorium recommendations. However, we must keep in mind that out-patient chemotherapy has a place in treatment, and there are many advantages in restoring the home life of the patient and shortening the period and cost of hospitalisation.

Throughout Canada and the United States patients leaving sanatoria against medical advice have become an increasing problem. The new drugs to some extent have aggravated the situation because of their prompt effect upon symptoms and the patient's well-being. Also, by rendering sputum negative for tubercle bacilli early in treatment, legal hold from a public health point of view is weakened.

The ultimate goal of successful treatment is the restoration of the patient to economic independence and to maximum usefulness to himself and the community. To attain this objective the Sanatorium Board provided for patients in all sanatoria a rehabilitation service which consists basically of vocational counselling and academic, occupational and vocational training. There is little unemployment among ex-sanatorium patients."

50TH ANNUAL REPORT OF TORONTO HOSPITAL (FOR TUBERCULOSIS) 1953.

This Report, among other features, emphasises the recent trends in the treatment of tuberculosis. It deals with chemotherapy in tuberculosis with special reference to (*a*) combination of anti-microbial agents, (*b*) duration of chemotherapy, (*c*) chemotherapy and need for resectional surgery, (*d*) chemotherapy and disappearance of tubercle bacilli; the treatment of special forms of tuberculosis, such as tuberculous meningitis, miliary tuberculosis, genito-urinary tuberculosis, bone and joint tuberculosis and tuberculosis of lymph nodes. There are special paragraphs dealing with pulmonary resection, thoracoplasty, artificial pneumothorax and pneumoperitoneum, phrenic paralysis

and extrapleural pneumonolysis. From the surgical service, tuberculosis of bones and joints and their present treatment; present trends in thoracic surgery in relation to one-stage thoracoplasty; multiple-stage thoracoplasty; mortality in thoracoplasty and sputum conversion after thoracoplasty are all outlined. The indication for pulmonary resection, including pneumonectomy, lobectomy, segmental resection, lobectomy and segmental resection are all detailed and sputum conversions in relation to these resections are fully considered. The indications for decortication of the lung, with special reference to inexpansible lung after pneumothorax, is outlined and there is a careful analysis of the bronchoscopic examinations done in 1953. A further section deals with genito-urinary tuberculosis. The Report is well balanced and merits careful consideration.

NOTES AND NOTICES

TUBERCULOSIS EDUCATIONAL INSTITUTE

An intensive Postgraduate Course on " Tuberculosis and the Family Doctor " will be held at the Kingston Hospital and Chest Clinic, Kingston-on-Thames, on Saturday and Sunday, October 23 and 24, 1954, with clinical and X-ray demonstrations and a review of pathological methods. The lecturers will include: Dr. J. V. Hurford, Dr. C. H. C. Toussaint, Dr. S. R. Wilson, Dr. D. Stark Murray and Mr. Robert Laird.

INTERNATIONAL COURSE ON TOMOGRAPHY

The third international Course on Tomography will be held at the Institute of Radiology in the University of Genoa at the end of September 1955, under the direction of Professor A. Vallebona. The course will last ten days and will deal more particularly with recent progress in methods of Tomography.

N.A.P.T.

The Fourth Commonwealth Health and Tuberculosis Conference is to take place at the Royal Festival Hall, London, from June 21 to June 25, 1955. Lectures, Discussions and Clinical Meetings, as well as Practical Demonstrations and visits to Sanatoria, Hospitals and Clinics, are among the main features of the Conference.

We much regret that a printer's error occurred in our last issue which gave the erroneous impression that the Conference had in fact already taken place.

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Notice to Contributors

The British Journal of Tuberculosis and Diseases of the Chest is intended for the publication of papers on all aspects of tuberculosis, diseases of the chest and cognate subjects. Papers dealing with original work not previously published are especially invited.

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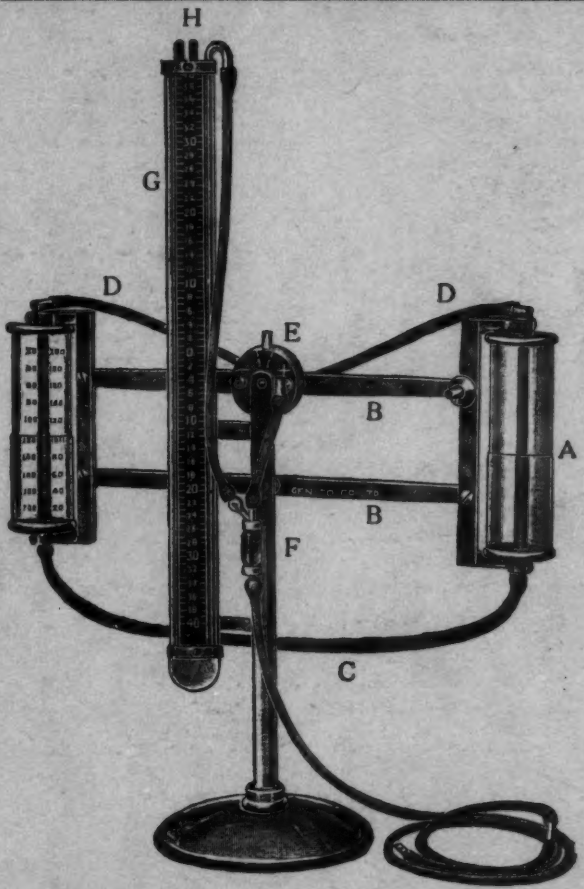

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